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THE PRESENT STATUS OF ORAL VACCINATION AGAINST POLIOMYELITIS AND FUTURE PROBLEMS

C. E. VAN ROOYEN, D.Sc., M.D.(Edin.), M.R.C.P.(Lond.), F.R.C.P.[C.],* and R. L. OZERE, B.Sc., M.D.,† *Halifax, N.S.*

THIS ARTICLE will discuss certain epidemiological, immunological and virological aspects of anti-poliomyelitis immunization in the light of current activity in the use of attenuated live oral vaccines.

First, we shall state the situation as it applies to poliomyelitis in North America. Thereafter, an account will follow of ecological considerations known to influence the acquisition of natural immunity in warm and cold climates respectively, compared with the development of artificial immunity after vaccination. A summary of work on live virus vaccine trials conducted in different areas of the world is presented.

EPIDEMIOLOGY

According to the statistical data of Langmuir,[1] it is reasonable to assume that field experience in the U.S.A. up to 1958 reveals an effectiveness of Salk vaccine against paralytic polio in the range of 90% or better. Protection conferred by the vaccine against the non-paralytic illness may be of lesser order. These findings are echoed by Kubryk,[2] who observed similar results in Canada. Examining these figures more closely, in the U.S.A. for the year 1959, and the week ending January 18, 1960, there were 8577 cases of poliomyelitis reported, of which 5094 were paralytic. Among the paralytic cases 3243 received no Salk vaccine, 439 received one dose, 486 received two doses, 772 received three doses, and 168 received four doses of vaccine. The protective effect of the vaccine against paralysis is therefore self-evident when one considers the population at risk.[3]

Poliovirus has a remarkable aptitude for selecting the so-called "soft spots", or areas of the U.S.A. where the population have neglected to avail themselves of the Salk vaccination program, and also for affecting mainly those of lower socio-economic status.[4]

The incidence of paralytic poliomyelitis in the U.S.A. and Canada for the year 1959 has been the greatest on record since 1956, e.g., up to the forty-fifth week of 1959, 5150 paralytic cases in the U.S.A. as against 6717 in 1956. The figure for Canada for the period ending November 14, 1959, was 1608 paralytic cases. This figure was exceeded only in 1953, which in turn was the greatest recorded since 1949.[5]

Simultaneously, a decline in the number of non-paralytic cases reflects the availablility of better virus laboratory diagnostic facilities for exclusion of Coxsackie, ECHO and other viruses of aseptic meningitis.[6] The present epidemic coincides with the predictable cyclical pattern of poliomyelitis incidence in North America over the past three decades and may explain the large number of cases encountered in the summer of 1959.

Resistance to Poliomyelitis through Process of Natural Infection

There is a difference between naturally acquired immunity to poliomyelitis through exposure to live virus and that developed after artificial immunization with formolized virus vaccine. The basic concept in the use of Salk vaccine has been to elevate the circulating serum antibody level in man, such as to alter his immunoreactivity, to the point at which it will protect the individual against viral invasion of the central nervous system and so against paralysis.[7]

Naturally acquired immunity is built upon an initial challenge through ingestion of virulent "wild" poliovirus, which may gain entry to the blood stream through the Peyer's patches of the small bowel.[8] In a small proportion of such individuals, for reasons not understood, the virus is capable of entering the central nervous system and causing paralysis. In the overwhelming majority of cases, however, the infection is inapparent and may be strictly localized to the cells of the intestinal wall. Viræmia has long been suspected as the primary route of invasion of the central nervous system in paralytic poliomyelitis. There is reason to believe, however, that it may be of relatively short duration,

*Professor of Bacteriology, Dalhousie University.
†Research Fellow, Department of Medicine, Dalhousie University.

since up to 1954, viræmia was demonstrated in only 14 instances, according to Davis and Melnick.[9] The incidence of viræmia in non-paralytic poliomyelitis is unknown. Opinion to the contrary contends that virus reaches the CNS via direct axonal spread, entering through the innervated superficial epithelial cells of the alimentary tract.[10]

The result of such initial exposure to virus is to produce a humoral antibody response followed by local tissue immunity or resistance of the gut wall to reinfection. The studies of Paul and Riordan,[11] in an isolated Eskimo community in Alaska, showed that infection with Type II virus could evoke an antibody response which was still detectable after 20 years, in the absence of intervening reinfection. However, recent work with attenuated live viruses suggests that the maintenance of higher levels of immunity in urban communities may be dependent on repeated subclinical infections.[12]

The acceptance of this concept acknowledges the existence of a reservoir of virus infection in nature, without which the natural process for the maintenance of herd immunity would be disrupted. The existence of paralytic poliomyelitis in a community may be likened to that of an iceberg; only the lesser number of paralytic cases are visible but the bulk of infections are concealed below the surface. It is possible that the subclinical infection is responsible for the perpetuation of infection and immunity among the population, and paralytic cases therefore represent a deviation from the usual host-virus relationship. Thus, according to Melnick and Ledinko,[13] after an epidemic from Type I polio at Winston-Salem, it was estimated that the number of clinically recognized cases was 10 to 16 per 1000 subclinical infections. At the present time, we may have at our disposal the means for displacing the world-wide reservoir of wild virulent viruses, by the artificial dissemination of attenuated live viruses amongst our population.

Poliomyelitis in the tropics.—Comparative studies on the pattern of tropical poliomyelitis have helped us to understand its immunology and may shed some light on its behaviour in temperate climates. During World War II attention was focused on the high attack rate of poliomyelitis among servicemen in tropical areas as opposed to the local inhabitants. These observations were made in Malta by Seddon *et al.*[14] and Bernstein, Clark and Tunbridge;[15] in Mauritius by MacFarlan *et al.*[16] and Seddon, Hawes and Raffray;[17] in Ceylon by de Silva;[18] in Singapore by MacFarlan;[19] and in Egypt by Paul, Havens and van Rooyen[20] and van Rooyen and Morgan.[21] These and subsequent workers, e.g. Gear,[22] have proved that although poliovirus appears to be hyperendemic in the tropics, the paradoxical situation exists wherein paralytic poliomyelitis has been historically uncommon among local inhabitants.

The age incidence of tropical, as opposed to temperate climate, poliomyelitis is well summarized by Rhodes.[23] The latter states that, in tropical climates, the disease is still primarily one of infants. Thus in the Malta, Mauritius and Singapore outbreaks, over 75% of cases were in children under five years of age. The majority of infantile cases were mild in character. Several explanations have been offered for the high case rate and mildness of the disease among infants in the tropics.

1. Whereas the bulk of the population has acquired immunity through contact with hyperendemic poliovirus, the infant group from age one to four years is relatively unprotected after the loss of maternally transferred passive antibody. Owing to poor conditions of sanitation and hygiene, at seasons of the year when sanitary conditions are at their worst, infants are liable to be challenged with large doses of poliovirus. The disease in these infants is, however, relatively mild and the explanation for this is that they acquire their primary poliomyelitis infection while still being partially covered by declining levels of maternal antibody.[24]

2. It has also been suggested that some protection may be transferred by breast milk. The mechanism of such immunity, if present, is not fully explained. It has not been possible to alter the infection rate in cynomolgus monkeys by feeding them human milk containing antibodies to poliomyelitis.[25]

3. In tropical areas the available reservoirs of polioviruses may consist of strains which are naturally attenuated, relative to the high antibody status of the local population. The high attack rate among service personnel entering these areas suggests that they were either completely devoid of antibody or else encountered for the first time virus antigenically dissimilar to that which they had experienced in their own country.

4. To the above three possibilities we would add that in the tropics the size of the available infant population at risk is relatively large and may account for infantile poliomyelitis in these zones. To this may be coupled the effects of higher infant mortality and the greater annual turnover in susceptible age groups.

Poliomyelitis in temperate climates.—In cool climates, epidemic paralytic poliomyelitis is more common than in the tropics, but there is reason to believe that the reservoir of virus is relatively smaller among the population. This paradoxical situation may be partially explained by the better hygiene of the population. Thus the date of primary exposure to virus is postponed from infancy to later on in life, so that the disease tends primarily to affect the 10-20-year-old and young adult age groups.[26] This assumption is further substantiated by comparative antibody surveys conducted in temperate and tropical populations. Turner *et al.*[27] showed that 78% of children in the vicinity of Baltimore from two to three years of age lacked Type II polio antibody, whereas only 28% lacked Type II antibody at five to nine years of age.

In Alaska, Paul and Riordan[11] demonstrated that nearly all Eskimo natives below the age of 20 years, from two villages, lacked antibody to Type II virus. In contrast to the above, Paul *et al.*[28] showed that in tropical Egypt 79% of the children had Type II antibody by the age of three years.

Thus, in Canada, it would seem that poliomyelitis is of low endemicity and high epidemicity with relatively high paralytic attack rates. The reason for this may be related to one or more factors, such as geographical terrain, climate, population density, virulence of virus strains, and improved hygiene and sanitation.[29] From modern virus isolation and serological typing techniques, it has been learned that Type I infection is the most important agent in temperate climates.

SALK VACCINATION

The underlying principle in the application of inactivated Salk vaccine has been, firstly, to stimulate the production of neutralizing antibodies in humans against all three types of poliomyelitis virus; secondly, to maintain such levels of antibody by repeated booster injections of vaccine so as to block the entry of virus to the CNS and so prevent paralysis; and, thirdly, to induce a state of immune hyperreactivity. Salk[30] has shown that there is wide fluctuation in the antibody response from one individual to another, as well as considerable variation in the duration and persistence of such antibodies. Circumstances point to a similar state of hyperreactivity or state of antibody avidity after immunization in nature.[31] It is postulated that this state of hyperreactivity, which may be enhanced by Salk vaccination or attained by repeated natural infection, permits a sufficiently rapid antibody build-up under the stimulus of natural infection to prevent the virus from penetrating the blood-brain barrier.

Bodian,[8] Fox *et al.*[32] and others have shown that Salk vaccination does not materially abolish the intestinal carrier state for wild strains of poliovirus. Thus, even if the entire world population were to receive Salk vaccine, it still might not arrest the natural epidemic spread of virus, though the paralytic attack rate would be appreciably reduced.

For complete protection against poliomyelitis, at least two factors are essential. The one is a serum neutralizing antibody level adequate to protect against paralysis, and the other, intestinal immunity or the capacity to eliminate the carrier state. The latter can be achieved only through ingestion of living virus.

ORAL VACCINATION WITH ATTENUATED VIRUS

During the years 1955 to 1959, when Salk vaccination was used in the U.S.A. and Canada, simultaneous research in the development of attenuated "live" orally administered vaccines against poliomyelitis was being conducted in the U.S.A. by Koprowski, Cox and Sabin. The earliest experiments, performed on the adaptation of virulent poliovirus to rodents and chick embryos, revealed that on occasion such procedures could produce strains of poliovirus which were less pathogenic on intracerebral inoculation of monkeys. These results induced Koprowski *et al.*[33] to try feeding such material to human subjects as an oral method of vaccination against poliomyelitis.

Further impetus was given to the study of attenuated poliovirus by the classic studies of Enders, Weller and Robbins,[34] who demonstrated that poliovirus could be grown in extra-neural tissue cultures. Another major step forward resulted from the discovery of Dulbecco and Vogt[35] that poliovirus could be induced to produce plaques on tissue cultures of monkey kidney overlaid with agar. By this technique, each plaque or clone represented growth from a single virus particle and was therefore genetically pure.

Later, tissue culture experiments revealed that mutant attenuated poliovirus strains which were of reduced neurovirulence for monkeys, could also be shown to exhibit certain *in vitro* characteristics apparently correlated with their apparent lack of neurovirulence. These factors, now labelled so-called "markers" of attenuation, combined to show that mutant attenuated poliovirus strains were less able to survive minor changes in their *in vitro* environment. For example, attenuated mutants of poliovirus produced small irregular-shaped plaques on tissue culture in a relatively acid medium.[36] Subsequently further mutant characteristics have been described, but these await the test of time and numbers before acceptance as parameters of diminished monkey neurovirulence. At the present time, attenuated strains of all three types of poliovirus have been developed by Koprowski, by Cox and associates, and by Sabin in the U.S.A. They have been fed to large numbers throughout the world.

Table I contains a summary of field trials of various attenuated live vaccines used in different areas.

History of vaccine strains. — When a virus is adapted to a new host, it frequently acquires added virulence for its new host and diminished virulence for the old.[37] This principle has been exploited as the basis for establishing attenuated mutant poliovirus for use as human vaccines. Dick and Dane[38] have summarized the historical background of the presently available live polio vaccine strains. Koprowski *et al.*[33] originally used a Type II strain designated TN, which had been attenuated for humans by passage in rodents. The passaged virus was also shown to be relatively avirulent for monkeys when injected intracerebrally. Koprowski's Type I SM strain virus was attenuated by passage in mice, and later in monkey and chick-embryo tissue culture, followed by further plaque purification techniques.[35] Sabin derived his vaccine strains from triply purified plaques, originally using strains selected for purity by terminal dilution

techniques. These strains were tested for attenuation by intraspinal inoculation of monkeys. From many plaque passages he selected a Type I strain designated L Sc, 2 ab. His Type II strain was similarly purified from a naturally occurring strain (P-712) which had been fed to a chimpanzee. Sabin's Type III strain[39] was developed from Leon virus. Cox *et al.*[40] used adapted animal passage and plaque purification to obtain vaccine strains, their Type I being derived from SM virus, Type II from mouse, hamster and chick-embryo adapted MEF_1 virus, and Type III a purified attenuated Fox strain originally isolated from a non-paralytic polio case.

The production of vaccine strains has included a battery of *in vitro* and *in vivo* tests for the purposes of eliminating contaminant bacteria, fungi, simian viruses, measles and enteroviruses.[41]

Human Feeding Experiments

Human feeding experiments in ever-increasing numbers have been in progress since 1956,[33] and Table I summarizes the extent of various field trials carried out to date. The vaccines have been variously administered to humans in liquid form, as a throat spray,[42] and in the form of gelatin-coated capsules.[41] Most of the experimental feedings have employed monovalent Type I or Type II virus, given sequentially at three to six week intervals, but several researchers have used trivalent (mixtures of Types I, II and III) forms administered in a single dose.[40, 43]

Tests of Attenuation and Criteria of Safety

Most tests of attenuation of vaccine strains have been based on demonstrating lack of virulence in rhesus or cynomolgus monkeys when injected intraspinally or intracerebrally. These animals are highly susceptible to paralysis by non-attenuated poliovirus when inoculated into the central nervous system, but at the same time they are relatively resistant to polio infection by the oral route. Recent tests by Murray *et al.*[44] have also used intramuscular injections to determine the presence or absence of monkey paralytogenic vaccine strains.

The monkeys, after intracerebral or intraspinal injection, are observed daily for signs of paralysis. Even in the absence of paralysis, however, spinal cords and brains are harvested after a specified time of observation of approximately four weeks, and sections are made for evidence of polio lesions in the spinal cord both at the site of injection and in remote segments.[45] Conflicting reports have been recently published on the results of monkey neurovirulence testing of various vaccine strains, some of the vaccines being apparently more paralytogenic than others.[39, 45, 46]

Although monkey neurovirulence is the most reliable test of attenuation at present, it has been suggested that the intraspinal test may be too sensitive and that strains sufficiently attenuated to produce no lesions on intraspinal injection of monkeys, may be equally low in antigenicity for use as human polio vaccines. The proof of this statement awaits the test of further research. Sabin[47] has shown that as one ascends the evolutionary scale of primates from monkeys, through gibbons, to chimpanzees, the species exhibit increasing susceptibility to poliovirus infection via the oral route and are correspondingly more resistant to infection by direct CNS inoculation. Theoretically, therefore, as an *in vivo* parameter of poliovirus attenuation for humans, the chimpanzee might be the animal of choice. However, the cost of these animals would be prohibitive. At the present time, therefore, monkeys remain the standard laboratory animal in testing vaccines for neurovirulence.

In vitro *criteria of attenuation — "mutant markers".* — Recently, other criteria to show the presence of mutant attenuated polioviruses have been developed, using *in vitro* tissue plaque culture techniques. Vogt, Dulbecco and Wenner[36] demonstrated that mutant attenuated strains of poliovirus had reduced efficiency of plaquing in tissue culture when the overlying medium was rendered more acid. The mutants grew more slowly, and tended to produce small, irregular plaques, in comparison with wild virulent strains. These findings correlated with tests of monkey neurovirulence,[45] although there has been some variation of reported results.[48] Kanda and Melnick[49] demonstrated that attenuated poliovirus strains were distinguished by small or absent plaques when grown on a stable (i.e. self-perpetuating) line of monkey kidney-cells. Similarly, Lwoff and Lwoff[50] demonstrated that attenuated strains grew poorly on tissue culture at a temperature of 40° C. Recent evidence by Melnick[45] suggests that this temperature factor may be a reliable *in vitro* marker of attenuation. It should be pointed out, however, that these markers have been developed recently, and they await the test of time and numbers before full evaluation of their importance can be achieved.

Antigenicity

Reports suggest that there is some variation in the ability of live vaccine strains to produce immunity in humans. This has depended to some extent on the area and climate of the field trials, the season, the age of the subjects, the vaccine strain used, and whether the vaccines were used singly or in triple combinations.[40, 51, 52]

Analysis of the available data on conversion rates from serum antibody negative to antibody positive indicates an effectiveness in the region of 90% in children where single-strain vaccines have been used, and perhaps somewhat less favourable results with single-dose triple-mixture preparations. Preliminary results reported on feeding infants under

TABLE I.—SUMMARY OF ATTENUATED ORAL POLIOMYELITIS VACCINE FIELD TRIALS IN OVER 13 MILLION PERSONS

Site of trial	*Numbers fed*	*Age group*	*Virus type fed: I, II, III*	*Vaccine used*	*Accidents reported during trial*	*Reference*
Minnesota	223	Pregnant women	Trivalent	Lederle-Cox	Nil	Prem and McKelvey (1959)[54]
Minnesota	39	Infants under 6 months	Trivalent	Lederle-Cox	Nil	Prem, McKelvey and Fergus (1959)[54]
Minnesota	551	Community	3 Types fed sequentially	Lederle-Cox	Nil	Barr *et al.* (1959)[57]
New Orleans	56 families	Children and adults	3 Types fed sequentially	Sabin	Nil	Gelfand *et al.* (1959)[58]
New York	550	Adults and children	3 Types fed sequentially	Lederle-Cox	Nil	Cox *et al.* (1959)[60]
New Jersey	46	Infants under 6 mos. and 13 adults	3 Types	Koprowski	Nil	Plotkin *et al.* (1959)[53]
Connecticut	24	Adults	Type I	Sabin	Nil	Horstmann *et al.* (1957)[48]
Connecticut	5	Adults	Type I	Sabin	Nil	Horstmann *et al.*)1957)[12]
Mexico	160,456	All children under 6 yrs.	3 Types	Sabin	Nil	Ramos-Alvarez *et al.* (1959)[51]
Costa Rica	80,912 67,594	Children and adults	Type II Type I	Lederle-Cox	Nil	Quirce *et al.* (1959)[59]
Cuba	2000	Children 4-17 yrs.	Trivalent and monovalent	Lederle-Cox	Nil	Embil *et al.* (1959)[60]
Nicaragua	59,855 54,732 49,585	Children	Type II Type III 3 Types	Lederle-Cox	Intercurrent Type II polio epidemic	da Silva *et al.* (1959)[61]
Uruguay	218,624	Children and adults	3 Types sequentially	Lederle-Cox	Nil	Leunda *et al.* (1959)[62]
Uruguay	26,442 29,676 40,000	Children and adults	2 Types 1 Type	Lederle-Cox	Intercurrent Type I polio epidemic	Leunda *et al.* (1959)[62]
Colombia Medellin	133,000	Children under 10 yrs.	3 Types sequentially	Lederle-Cox	Nil	Abad-Gomez *et al.* (1959)[63]
Colombia Andes	7378 7122 6977	Children under 7 yrs.	Type I Types I and II 3 Types	Lederle-Cox	Nil	Abad-Gomez *et al.* (1959)[64]
Northern Ireland	18 124	Adults Children	Type II Type II	TN Koprowski TN Koprowski	Nil	Dick *et al.* (1957)[65]
Northern Ireland	14	Children	Type I	SM Koprowski	Nil	Dane *et al.* (1957)[66]
	25	Infants	3 Types	Lederle-Cox	Nil	Dane *et al.* (1957)[58]
Netherlands	200	Children and adults	3 Types	Sabin	Nil	Verlinde and Wilterdink (1959)[67]
Sweden	20	Families	Type I	Koprowski-Chat	Nil	Gard *et al.* (1959)[68]
Finland	44	Adults and children	Type I	Lederle-Cox	Nil	Oker-Blom *et al.* (1959)[69]
Poland	2888	Under 17 yrs.	Type I	Koprowski-Chat	Nil	Przesmycki *et al.* (1959)[70]
Czechoslovakia	143,777	Children under 9 yrs.	3 Types	Sabin	Nil	Skovranek *et al.* (1959)[71]
Russia	1,800,000	Under 16 yrs.	3 Types	Sabin	Nil	Smorodintsev *et al.* (1959)[43]
Russia	10,000,000	Mostly under 15 years of age	3 Types	Sabin	Nil	Chumakov (1959)[72]
Ruanda Urundi	250,000	Children and adults	Types I and III	Koprowski	Intercurrent epidemic	Courtois *et al.* (1958)[73]
Belgian Congo	75,000	Under age 5	Type I	Koprowski	Nil	Lebrun *et al.* (1959)[42]
Singapore	198,965	Under 11 yrs.	Type II	Sabin	Intercurrent Type I polio epidemic	Hale *et al.* (1959)[74]

Total number of persons fed with attenuated polioviruses—13,416,902.

the age of two months, according to Plotkin, Koprowski and Stokes,[53] and da Silva *et al.*,[52] may suggest a relatively poorer response, although the work of Prem, McKelvey and Fergus[54] fails to confirm this view. A similar poor response with "dead" vaccine has been noted by Perkins.[55] Antibody conversion rates or booster effects in immune adults have also been variable. It would seem, so far, that the best results with live vaccine, as measured by serum neutralizing antibody, have been in antibody-negative children over the age of one year.

However, in polio immunity, another important aspect must be considered, namely, the ability of the gut wall to reject repeated poliovirus infection as measured by detectable and prolonged stool virus excretion, i.e. "intestinal immunity". This latter can be acquired only through a process of active intestinal infection by virus. Thus, in determining whether or not a subject has been successfully vaccinated, one must consider not only the serum antibody response, but also laboratory proof of intestinal infection by demonstrating virus in stools. Additional proof of intestinal immunity might be demonstrated by the ability of the successfully vaccinated individual to resist intestinal infection after re-feeding with homotypic attenuated virus. Likewise the duration of immunity in vaccinees could perhaps be best established by measuring the ability of the gut to reject reinfection by vaccine virus at future dates after proved immunization, rather than by measuring the rate of decay of serum antibody alone.

Safety

Table I reveals that over 13 million persons have been fed various vaccine strains without harmful effects. These field trials include some 12 million Russians who have been fed the Sabin vaccine as well as vaccine prepared in Russia.[72] On the ground of numbers fed, therefore, there would seem to be little doubt concerning the safety of the vaccines used. At the time of writing, extended trials are contemplated in the U.S.A. using Lederle-Cox and Sabin vaccines in Florida and New York respectively. The protective value of these vaccines has not yet been established, but it is hoped that the large numbers fed in Russia, South America, Minnesota, New York and Florida will provide the answer. From the epidemiological point of view, the danger of developing poliomyelitis from oral vaccine is small. On the contrary, much greater risk is incurred by unvaccinated persons exposed to wild virus, particularly those resident in fringe population areas in the proximity of vaccine trials.

Contact Spread

The virus vaccines for poliomyelitis are the first viral vaccines to be administered orally; moreover, they are the first vaccines capable of spread by contact, from person to person. Sabin,[39] Koprowski,[33] Dane *et al.*,[66] Horstmann *et al.*,[48] Gelfand *et al.*,[58] and others have shown unequivocally that spread of virus has occurred between vaccinees and contacts, especially in institutional feeding trials. The use of these products has been the subject of considerable controversy and apprehension by Dick *et al.*[65] Gelfand *et al.*,[58] in a well-controlled experiment, studied 56 household units of varying socio-economic levels and degrees of sanitation. They studied the degree of spread of fed virus, using Sabin's Type I, II and III, between members in families and neighbouring families. Each of the family units contained at least three naturally susceptible members, only one of whom was fed the vaccine. The most sensitive index of contact spread was determined by stool virus excretion, and the ratio of family contact infection varied from none out of five to 13 out of 15 persons, depending upon the socio-economic status, crowding, and sanitation of the household units studied. Pharyngeal virus excretion was detected in a number of the fed persons, but was much less consistently present than stool excretions. Of susceptible contacts from the upper socio-economic group 9% became infected as compared with 53% in lower socio-economic households. Contacts excreted virus from one to 41 or more days. These experiments were conducted using monovalent strains of vaccine. There was a suggestion of interference to virus spread by the presence of other "wild" enteric viruses in certain households, especially in the lower economic brackets.

In an island study in Finland, using a Type I vaccine, Oker-Blom *et al.*[69] found a 35% spread in unvaccinated contacts. Przesmycki *et al.*[70] in Poland, using a monovalent Type I vaccine in 2888 children, estimated the contact spread at 17% in institutional trials. Kleinman,[75] using a trivalent vaccine, estimated the contact spread at 14% in his series. There may be some early evidence, therefore, that a trivalent vaccine, by virtue of possible interference effects, may have less tendency to spread to adjacent contacts.

Genetic Stability of Live Vaccines

The principal objections to the use of live vaccines have been based on the demonstration by Melnick, Melnick and Brennan,[45] Dick *et al.*,[65] Horstmann *et al.*,[48] and others, that some of the mutant attenuated strains tended to revert to monkey neurovirulence or increased monkey neurovirulence, after contact passage through human intestine, or after prolonged excretion in a fed individual. Refeeding experiments on humans, using repeatedly human-passaged stool vaccine virus by Koprowski,[76] have indicated some reversion to monkey neurovirulence which apparently reached a plateau after two or three passages in humans, and retained a large degree of attenuation thereafter. Dick and others[65] have objected to the wide dissemination of live vaccines as presently constituted, on the basis of this evidence of some lack of stability of the vaccine strains after human contact passage. They feel that the viruses show a definite tendency to reversion (i.e. instability) towards neurovirulence, and therefore widespread use might result in the build-up of a large reservoir of "reverted" virulent poliovirus, which would constitute a threat to the susceptible members of a community. This threat would apply in particular to areas adjacent to large-scale field vaccination trials.

In reply to these objections, it has been argued by the proponents of live vaccine that the world reservoir of wild poliovirus consists of a spectrum ranging from naturally attenuated mutants to highly virulent strains, and that the effect of using attenuated vaccines would be to increase the attenuated portion of the spectrum, displacing the virulent form, and so help to perpetuate natural immunity in the world population. This viewpoint holds that the "epidemic" character of the vaccine is perhaps not disadvantageous.

From the above, it would seem that some of the pressing needs for research in this field are (a) to determine whether vaccines are as contagious as "wild" strains—preliminary evidence of Gelfand *et al.*[58] indicates that they are less so; (b) to determine through how many human contact passages vaccine strains can survive; and (c) to determine whether, in repeated passage, the vaccine strains revert to neurovirulence and become "wild" in all respects so that they are no longer recognizable by laboratory methods as the original vaccine strain. McBride[77] showed that tested strains of poliovirus had a neutralization constant (k), i.e. rate of neutralization, when measured against homologous low-avidity typing sera. This factor could possibly be used as a marker of identification in separating vaccine from wild strains in field studies. Research on this aspect is at present under way. As far as we are aware, it is not known at present whether mutant "reverted" vaccine strains would retain their identity in this respect. Strain tagging studies, perhaps using the immune inactivation techniques of Gard,[78] against standard antisera could be invaluable.

If attenuated vaccines against measles, and other viral diseases, are to follow in the future, the need for distinguishing in the laboratory between wild and vaccine strains of virus should assume increasing importance.

Viral Interference between Poliomyelitis Viruses and Enteroviruses and Competition between the Three Types of Polioviruses

Under natural conditions it is possible that competition exists among viruses for available cell space

in the epithelial lining of the human gut wall. The possibility of interference between enteroviral agents sufficient to hamper the efficiency of oral vaccination with attenuated polioviruses has been reported by Paul *et al.*[79] They suspect that ECHO I virus may have interfered with successful oral immunization at trials at Guadalupe Village, Arizona. Likewise, Gelfand *et al.*[58] encountered interference during feeding trials with Sabin's vaccine from ECHO virus Types 7, 3, 6, 9 and 11, and Coxsackie virus Types A9 and B5 and unidentified adenoviruses. Apparently similar interference effects were encountered by Melnick *et al.*[45] during feeding trials in Mexico. Our own unpublished studies on an outbreak of 170 cases of paralytic poliomyelitis in Newfoundland, as well as observations on sporadic cases occurring in Nova Scotia, have revealed on several occasions the existence of concurrent ECHO virus and wild poliovirus infection in single families. These observations were noted as the result of a systematic search for viral carriers in the siblings and family contacts of all cases of paralytic poliomyelitis reported in Nova Scotia in 1959. Much further research is required to elucidate the mechanisms of enteroviral interference, if such should exist.

Deliberate attempts to displace wild virus by oral vaccine and so halt the progress of polio epidemics have been tried by several workers. The displacement of a Type I epidemic in Singapore by feeding the population Sabin's attenuated Type II vaccine, by Hale *et al.*,[74] was favoured with some success. Likewise, others attempted to show that the feeding of homologous type vaccine in the face of epidemics could halt the spread of wild paralytogenic virus through interference effects. Epidemic control of this nature was attempted in Nicaragua by da Silva *et al.*,[61] in Ruanda Urundi by Courtois *et al.*,[73] and in Uruguay by Leunda *et al.*[62] Much further work is necessary to establish these claims. The theoretical possibility of exaltation of virulence of poliovirus by summation effects with Coxsackie A infection has been suggested by Dalldorf and Weigand.[80] An important contribution to the field of viral interference has been the discovery of "interferon" by Isaacs and Burke.[81]

Summary

The future control of epidemic poliomyelitis would appear to be through the displacement of wild virus by mass feeding of the population with attenuated virus. This same principle has been and could be employed as a procedure for attempting to halt the spread of epidemics. Over 13 million persons have received attenuated virus without untoward effect. Objection to its continued use on the grounds of exaltation in monkey neurovirulence after human contact passage, may prove to be more a theoretical than a practical disadvantage. Evidence suggests that enteroviruses prevalent in summer time may interfere with a "take" by live poliomyelitis oral vaccine. Therefore, Salk vaccine, being an injectable product, possesses an obvious advantage in this respect.

Since Type I virus is the prevalent and virulent epidemic strain in North America, both the live vaccine and Salk vaccine should have strong specific antigenicity against this virus type. In the oral vaccine, if a trivalent product is to be used, it should be balanced in such a way that Types II and III will not interfere with a "take" by Type I.

For a successful program, the live virus should be applied uniformly throughout the entire population. Failure to vaccinate infants will shift the normal age susceptibility group in North America so as to create a situation similar to that pertaining in the tropics, where infants constitute the most vulnerable segment of the population.

In the existing state of knowledge it is difficult to predict what will be the most effective and durable future immunization schedule against poliomyelitis. Perhaps the use of an attenuated poliomyelitis vaccine will necessitate booster doses. The process of artificial infection may have to be repeated more frequently to maintain the level of herd immunity comparable to that derived from natural "wild" virus infection.

To overcome possible enteroviral interference effects in large-scale oral vaccination programs, Salk vaccine should be continued, especially in the infant group under two years of age. For the same reason, live virus programs, when initiated, should be conducted during the winter months.

The choice of strains to be used in live vaccine is important. The present emphasis and quest for more avirulent strains might lead to the adoption of vaccine strains sufficient for the purpose of displacing wild virus but inadequate for the maintenance of long-term herd immunity. The use of such strains over a period of several years could result in progressive deterioration of the antibody status of the population, with a corresponding increase in susceptibility to virulent poliomyelitis virus.

Since the epidemiology of poliomyelitis differs between tropical and temperate climates, the results of oral vaccine field trials conducted in the former are not necessarily applicable to the latter. Before mass immunization with live virus can be attempted in Canada, extensive field trials with integrated laboratory studies are necessary to ensure genetic stability, antigenicity, and avirulence under our normal living conditions.

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RÉSUMÉ

L'avenir du contrôle de la poliomyélite épidémique semble appartenir au déplacement du virus nuisible par l'apport massif à la population de virus atténué. Ce principe a déjà été employé dans l'enraiement des épidémies et pourrait encore servir. Plus de 13 millions de sujets ont déjà reçu oralement du virus atténué sans effets fâcheux. L'objection à son usage prolongé, fondée sur une recrudescence de la neuro-virulence chez le singe après passage chez l'humain, semble un inconvénient plus spéculatif que réel. On a raison de croire que la profusion saisonnière des entéro-virus au cours de l'été nuirait à la "prise" du vaccin oral à base de virus vivant. Le vaccin Salk administré par injection possède donc un avantage indéniable à cet égard.

Comme le virus de type I forme la souche prédominante et virulente des épidémies en Amérique du Nord, il importe donc que le vaccin à base de virus vivant et aussi le Salk possèdent un fort pouvoir antigénique contre lui. Toute préparation orale trivalente devra être composée de manière à ce que la présence des types II et III ne s'interpose pas à la "prise" du type I.

Pour en assurer le succès, un programme de vaccination fondée sur l'emploi de virus vivant doit être appliqué à la population entière, car ne pas vacciner les jeunes enfants équivaudrait à déplacer l'âge des groupes de sujets susceptibles et créer une situation semblable à celle que l'on rencontre dans les tropiques où les enfants âgés de plus d'un an, constituent le segment le plus vulnérable de la population.

Dans l'état présent de la question, il est difficile de prédire quel sera le plan d'immunisation le plus efficace et le plus durable contre la poliomyélite. L'emploi d'un vaccin oral à base de virus poliomyélitique atténué exigera peut-être des doses de rappel. Le procédé d'infection artificielle devra-t-il être répété fréquemment pour conserver un degré d'immunité collective comparable à celui que confère l'infection naturelle et virulente?

Afin de surmonter la compétition entéro-virale qui pourrait s'opposer à la grande diffusion de l'application de la vaccination orale, on devra continuer à employer le vaccin Salk chez les enfants de moins de deux ans. Pour la même raison, la vaccination orale devra être pratiquée pendant les mois d'hiver. Le choix des souches employées dans le vaccin oral à base d'organismes vivants est d'importance primordiale. Les efforts déployés dans la recherche de souches avirulentes pourraient résulter dans la composition d'un vaccin comprenant des souches capables de déplacer le virus naturel mais incapables de produire une immunité collective durable. Cet état de choses se prolongeant pendant plusieurs années pourrait causer une détérioration progressive de la réserve d'anticorps de la population et mener à une augmentation de sa susceptibilité à la forme poliomyélitique virulente.

Puisque l'épidémiologie de la poliomyélite des régions tropicales diffère de celle des régions tempérées, les résultats de la vaccination orale obtenus dans celles-là ne sont pas nécessairement applicables à celles-ci. Il faudra donc procéder à des essais multiples et étendus, secondés d'études de laboratoire, afin de garantir la stabilité génétique, l'antigénicité et l'avirulence dans notre milieu de toute souche de virus vivant servant à la vaccination orale massive de la population.

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CHYMOTRYPSIN IN CATARACT SURGERY

HOWARD REED, M.B., M.S.,
F.R.C.S.(Eng. & C.),* *Winnipeg, Man.*

THE INCREASING use of enzymes is one of the most interesting developments in modern medicine. Streptokinase and streptodornase[1] seem to be of value in reducing traumatic œdema and hæmorrhage and in the control of inflammatory swelling in infection. Several observers have reported favourably upon fibrinolysin as an agent for dissolving intravascular clots[2] although this drug tends to cause pyrexia. Trypsin has been used to reduce swelling due to hæmorrhage and inflammation.

The discovery of the value of chymotrypsin in eye surgery is intriguing. It was the result of a clinical experiment, an unusual observation and a brilliant deduction. In May 1957, Barraquer injected chymotrypsin into the vitreous of an eye blind for some time owing to a dense vitreous hæmorrhage which failed to absorb. He hoped that the enzyme would aid the disappearance of the blood, but, on examining the eye soon after, he found, to his surprise, that the lens was dislocated. He was quick to appreciate the possibilities of the use of the enzyme in cataract surgery. He carried out a series of experiments on animal eyes and demonstrated that chymotrypsin has a specific lytic effect upon the suspensory ligament of the lens without apparently damaging the vitreous or other ocular tissues.

He began to use the enzyme in cataract extractions and reported his results to the Royal Academy of Medicine in Barcelona in 1958.[3] Since then numerous accounts of its use have appeared in the literature. On this continent, however, it is still in an experimental stage and until recently the enzyme was available to eye specialists for experimental study only.

THE DEVELOPMENT OF CATARACT SURGERY

A brief review of the main stages in the development of the modern cataract operation will assist in understanding the value of chymotrypsin.

In 1752, Daviel[4] described the extracapsular operation (Fig. 1). He made an incision at the edge of the cornea with a triangular-shaped blade. The incision was then enlarged with scissors. The anterior capsule of the lens was cut and the cataract was pushed out of the eye through the incision. This left behind the zonule and the posterior capsule of the lens which together formed a diaphragm separating the aqueous from the vitreous (Fig. 2). The disadvantage of this operation was that it tended to leave soft lens matter behind. This frequently irritated the eye so

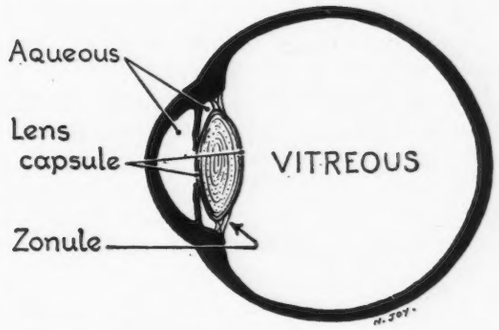

Fig. 1.—Anatomy of lens capsule and zonule.

that it became inflamed and later developed a secondary cataract.

In 1903, Smith introduced an improvement upon the extracapsular method, which is known as the intracapsular operation (Fig. 3). He ruptured the zonule of the lens by pressing upon the eye with a hook. The lens was then pushed out of the eye in its capsule. In his hands the operation was

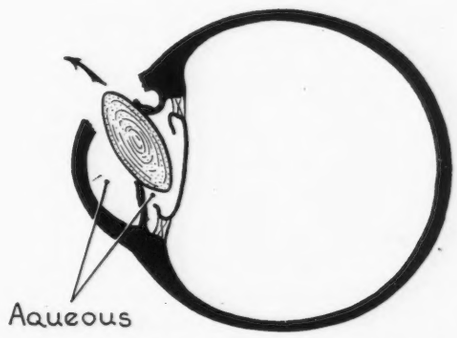

Fig. 2.—Extracapsular cataract extraction leaving an intact diaphragm of the posterior lens capsule and zonule separating the aqueous from the vitreous.

satisfactory but other less dexterous surgeons found the manœuvre difficult. Various modifications were made, and just before the last war the intracapsular operation became more popular. It was found that the zonule was ruptured more readily by grasping the lens capsule with forceps and combining a gentle pull on the capsule with pressure upon the outside of the eye.

An erisiphake was then introduced which consisted of a little suction cup. A small rubber bulb,

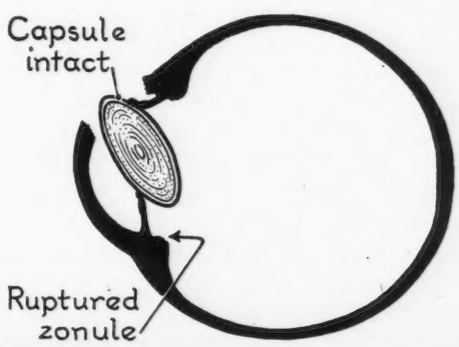

Fig. 3.—Intracapsular cataract extraction showing rupture of the zonule. The lens is contained in the intact capsule.

*From the Departments of Ophthalmology, University of Manitoba, Winnipeg General Hospital and Winnipeg Clinic.

like that of an eye dropper, was attached to it. This was compressed to expel the air. The cup was then applied to the anterior surface of the lens and a partial vacuum caused the capsule to be sucked into the cup of the erisiphake. This permitted more gentle grasping of the capsule than is possible with the capsule forceps. It was not entirely satisfactory, however, because the degree of suction was difficult to control. This difficulty was solved by Barraquer, who connected the erisiphake to a vacuum pump which controlled the degree of suction exactly.

Unfortunately in these intracapsular techniques the capsule occasionally ruptured before the zonule. If the capsule ruptured, the lens was incompletely extracted and soft lens material remained behind. As in the extracapsular operation, this caused irritation and inflammation, and the lens material often became opaque and occluded the pupil. The younger the patient the more likely was the capsule to rupture. This was particularly so under the age of 40. In fact, before the advent of chymotrypsin few operators would attempt an intracapsular extraction in a patient less than 40 years of age.

The use of chymotrypsin has solved the problem of capsule rupture but it involves some changes in the technique of extraction. Chymotrypsin lyses the zonule so that instead of the lens being firmly held in position by an intact zonule, it is dislocated and lying free on the surface of the vitreous. There is, therefore, no need to rupture the zonule by traction, which is the essential step in the usual intracapsular operation. The dislocated lens merely requires careful removal.

I have been using the enzyme for nearly two years and have employed it in 106 cataract extractions. A review of my results and experience will be presented.

OPERATIVE DETAILS

Since a visit to Barraquer's Clinic in 1957 I have been using his method of cataract extraction. The pupil is dilated with homatropine 2% eye drops. The eye is prepared in the usual manner and pontocaine 0.5% eye drops are instilled. Meperidine 75 mg., atropine 1/150 grain, and promethazine 15 mg. are given hypodermically half an hour before operation. Anæsthesia is induced by intravenous thiopental and 1 to 2 c.c. of gallamine (Flaxedil) is given during the operation. As soon as the patient is anæsthetized, a retrobulbar injection of 2% procaine with hyaluronidase is given and intermittent pressure applied to the eye for a few minutes until the eye is very soft. A soft eye is essential to minimize the danger of vitreous loss.

The incision is made with a cataract knife, making a moderately large conjunctival flap on cutting out. Two peripheral iridectomies are performed. The chymotrypsin is then squirted through the peripheral iridectomies with a lachrymal cannula. The cannula is not passed into the iridectomies. The iris can be seen to lift as the enzyme flows around the posterior chamber between the iris and the equator of the lens. One subconjunctival corneoscleral suture is then inserted while the enzyme is acting upon the zonule. When the zonule has disintegrated, the upper equator of the lens moves forwards and produces a slight elevation of the iris. This occurs in two to three minutes. After three minutes the anterior chamber is irrigated with normal saline to remove the excess enzyme. The Barraquer erisiphake is then applied to the lens, and the vacuum pump is switched on with the foot. The vacuum pressure is allowed to build up to about 150 mm. of mercury and the lens is then lifted out of the eye. Four or five subconjunctival corneoscleral silk sutures are then inserted using natural silk and Grieshaber needles. The pupil is constricted with a few drops of carbachol and air is injected to reform the anterior chamber. The conjunctival flap is closed with three or four interrupted silk sutures. Only one eye is padded. The patient is allowed out of bed the next day. Most patients are discharged on the eighth postoperative day.

RESULTS

When the enzyme chymotrypsin became available,* it was used in 83 cases. Quimotrase was used in 23 cases and it appeared to be equally effective. Thus the enzyme was used in 106 cases altogether.

TABLE I.

	Number of patients
Chymotrypsin—1 in 10,000	83
Quimotrase—1 in 5000	23
Enzyme used—total	106
No enzyme used	107
Total	213

During the same period I performed 107 extractions without enzyme. Normally no selection was applied to the cases, the deciding factor being the availability of the enzyme. Exceptions to this rule were made in regard to five patients aged 23, 28, 30, 32 and 36 years respectively. Their operations were delayed until a supply of enzyme was received and in each case the lens was extracted with ease.

A. *Complications at Operation*

TABLE II.—COMPLICATIONS AT OPERATION

	Enzyme	*No enzyme*
Ruptured capsule	1	8
Vitreous loss	4	1

One capsule was ruptured when the enzyme was used and eight were ruptured when it was not used. Vitreous loss occurred in four cases when

*Supplied by Armour Brothers.

the enzyme was used and in only one when it was not used. I should mention that in two cases of vitreous loss occurring with chymotrypsin the vitreous was fluid, one patient having advanced retinitis pigmentosa and the other high myopia. A third patient had advanced closed angle glaucoma. The fourth patient had chronic heart failure and cyanosis from a septal defect, and the anæsthetists were reluctant to give her a general anæsthetic. The first cataract in this patient was removed without difficulty but normal vitreous was lost during the operation on the second eye.

B. *Early Postoperative Complications*

TABLE III.—EARLY POSTOPERATIVE COMPLICATIONS

	Enzyme	*No enzyme*
Hyphæma	4	4
Flat anterior chamber	5	7
Choroidal detachment (up to 3 or 4 weeks)	3	1
Expulsive hæmorrhage (on 12th day)	0	1
Iris prolapse	0	0

The early postoperative complications appeared to be approximately the same in both groups. Striate keratitis was minimal and did not persist beyond the third or fourth day.

C. *Late Postoperative Complications*

TABLE IV.—LATE POSTOPERATIVE COMPLICATIONS

	Enzyme	*No enzyme*
Uveal pigment disturbance and iritis	0	0
Retinal detachment	1	0
Glaucoma	0	0

In one case in which enzyme was used retinal detachment occurred nine months after the operation. I cannot, of course, say whether the use of enzyme was a significant factor in this case.

VISUAL RESULTS

TABLE V.—VISUAL RESULTS

	Enzyme	*No enzyme*
Corrected visual acuity of 20/30 or better	89	80
Corrected visual acuity worse than 20/30	11	23
No postoperative refraction done	6	4
Total	106	107

Although the visual results in those patients treated with chymotrypsin appear to be better than those in whom it was not used (Table V), the difference is explained entirely by the fact that in the latter group there were more diseases such as degeneration of the macular area of the retina (Table VI). These diseases were unrelated to the use of chymotrypsin. It is, therefore, apparent that chymotrypsin has no serious effect upon the final visual result.

TABLE VI.—CAUSES OF DEFECTIVE SIGHT

	Enzyme	*No enzyme*
Macular degeneration	1	7
Myopic macular degeneration	1	5
Glaucomatous optic atrophy	5	4
Corneal dystrophy or scarring	3	3
Amblyopia due to untreated squint	0	2
Capsular remnants in pupil	0	1
Retinal detachment	1	0
Expulsive hæmorrhage 12 days after operation	0	1

COMMENTS

Murray and Drance[5] emphasized the necessity of a soft eye when using chymotrypsin. This cannot be overemphasized. Every measure for reducing the intraocular pressure should be employed. My own preference is for general intravenous anæsthesia by thiopental combined with gallamine triethiodide (Flaxedil), which reduces intraocular pressure. In addition, retrobulbar anæsthesia with hyaluronidase and massage are essential.

All writers agree that chymotrypsin acts upon the zonule so that the lens may be removed intracapsularly with ease even in the difficult age group of 20 to 40. In 106 cases in this series the capsule was ruptured on one occasion only. This was owing to the fact that the incision was too small, a fault in technique unrelated to the use of the enzyme.

Opinions differ somewhat on whether the use of chymotrypsin increases complications such as delayed wound healing, iris prolapse, vitreous loss, postoperative striate keratitis and iritis. In this series these complications appeared to occur with the same frequency whether the enzyme was used or not. There was no evidence that the enzyme damaged other tissues in the eye to any serious degree (Tables III and IV).

Barraquer[6] has noticed an increased incidence of subconjunctival drainage so that a conjunctival bleb persists for several days after operation. He thinks that this might be an indication of delayed wound healing and has, therefore, started to make a more scleral incision. But he is accustomed to sealing all bleeding points with electro-cautery before closing the wound and it might well be that this conjunctival bleb is due, not to aqueous filtration, but to reaction to the cauterization. This complication was not a problem in this series.

Some observers[5, 7] have reported that corneal reactions such as œdema, striate keratitis, and even vascularization may occur after the use of the enzyme. This was certainly not so in this series, or in Barraquer's.[6] The usual method of introducing the enzyme is to pass the cannula behind the iris at the 6, 9 and 3 o'clock positions in the region of the suspensory ligament. It is my practice merely to squirt about 1 c.c. of the enzyme through the two peripheral iridectomies. It does not seem necessary to pass the cannula into the iridectomies.

One of the dangers when using the enzyme is that since the lens is dislocated, the attempt to grasp the capsule with forceps may result in pushing the lens back into the vitreous. In order to avoid this

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some authors have suggested grasping the capsule with forceps before injection of the enzyme and holding on to the capsule until the zonule is lysed and the lens dislocates. It may be that multiple manipulations and folding of the cornea are the cause of excessive corneal reaction.

My series has an increased incidence of vitreous loss and this has occurred in the experience of other authors. Murray[5] and others have commented that the enzyme increases the tendency to vitreous loss, particularly in eyes with a fluid vitreous. Three minutes after the injection of the enzyme, the lens is usually completely dislocated and lying on the vitreous face. The slightest pressure on the lens at this stage can readily rupture the vitreous face, cause vitreous loss and even force the lens back into the vitreous itself. Intracapsular forceps and even the Bell erisiphake are liable to do this and their use is unwise. The danger is much less with the mechanical erisiphake. Its cup may be allowed to rest gently on the surface of the lens and the vacuum pump may be turned on with the foot switch without the slightest pressure on the lens. It is therefore essential to use the mechanical erisiphake with chymotrypsin. The danger of vitreous loss can be overcome only by using all measures to reduce the intraocular pressure, by making the minimum number of intraocular manipulations, and by exercising great gentleness in the manœuvre.

Barraquer[6] no longer uses the enzyme when doing a cataract extraction on patients over the age of 60, because by this age the zonule has become relatively friable and he considers it to be unnecessary. There is much truth in this view, but there is no doubt that the enzyme does lyse the zonule, and since the aim of the modern cataract operation is to remove the lens without rupturing its capsule, it seems that one should use all aids to this end. The enzyme does not appear to increase complications to any significant degree, so that it would appear to be wiser to use the enzyme even in the elderly.

Most writers have agreed that the enzyme should not be used on patients under the age of 20. I have had no experience of its use in such young patients. Barraquer,[6] who has had a greater experience than any other operator, considers that a dextrous surgeon may obtain good results in patients aged from 10 to 20, but that under the age of 10, zonulysis renders extraction hazardous.

Despite a few faint warning voices, the majority of writers[6, 8-11] agree that chymotrypsin is a most valuable aid to the performance of an intracapsular cataract extraction. In fact, it is probable that its use will increase and a decade hence few cataract operations will be performed without it.

CONCLUSIONS

Chymotrypsin represents a great advance in cataract surgery, because the cataract can be removed in its capsule in almost 100% of cases even in patients between the ages of 20 and 40. Complications are not significantly increased by its use. All measures for reducing the intraocular pressure preoperatively should be used. A mechanical erisiphake is essential for extraction after zonulysis.

SUMMARY

The recent discovery that chymotrypsin lyses the suspensory ligament of the lens is described. The stages of development of the modern intracapsular cataract operation from the original extracapsular operation are briefly reviewed. The use of chymotrypsin in the modern operation is described. The results of 106 cataract extractions in which the enzyme was used are presented and compared with the results of 107 similar operations performed without it. It is concluded that the use of chymotrypsin is an advance in cataract surgery. It makes the operation easier and complications do not appear to be increased by its use.

My thanks are due to Dr. Keith Grant, anæsthetist at the Winnipeg General Hospital, for his skill and cheerfulness when giving the anæsthetics to the patients on whom I have operated, and to Miss Lewicki and Miss Suwala, who are so attentive to my needs in the operating room. I am grateful to Miss Nancy Joy of the department of surgery, University of Manitoba, for the illustrations, which are reproduced by the courtesy of the *Manitoba Medical Review*.

I wish to express my gratitude to Dr. J. A. Hubata, Medical Director of Armour Pharmaceutical Company, Chicago, for supplies of chymotrypsin and to the Nova Drug Company in Montreal, for supplies of Ophthalmic Quimotrase.

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RÉSUMÉ

En mai 1957 Barraquer cherchant à faire disparaître une forte hémorragie de l'humeur vitrée injecta de la chymotrypsine et découvrit à sa surprise qu'il avait causé une dislocation du cristallin. L'expérience lui montra l'action spécifique de cette enzyme qui dissout les ligaments suspenseurs sans affecter les autres structures. L'auteur offre un rappel des principaux stages dans l'évolution de l'extraction de la cataracte commençant avec Daviel qui en 1752 décrivit l'intervention extra-capsulaire. La modification de Smith en 1903 en fit une opération intra-capsulaire. L'introduction de la chymotrypsine a supprimé les complications que présente la rupture de la capsule au cours de cette intervention par dissolution de la zonule. L'auteur a recouru à cette méthode pour 106 opérations depuis près de deux ans et il fait part de son expérience en comparant cette série à une autre composée de 107 extractions pratiquées avec les méthodes habituelles au cours de la même période de temps. Sa technique opératoire est décrite en détail. L'enzyme ne doit être employée que dans un globe mou, il convient donc de réduire la tension intra-oculaire le plus possible. Une fois la zonule dissoute, on procède à l'extraction avec un érésiphaque mécanique. Les complications postopératoires ne sont pas augmentées par l'usage de ce médicament; cependant il semble préférable de ne pas l'employer chez les sujets de moins de 20 ans.

ALPHA-CHYMOTRYPSIN IN CATARACT SURGERY*

DEREK G. SIMPSON, F.R.C.S.,
Vancouver, B.C.

BARRAQUER'S[1] performance of enzymatic zonulysis, first reported to the Academy of Medicine of Barcelona in April 1958, and then to the French Ophthalmic Society in May 1958,[2] has aroused world-wide interest. In an article in the *Klinische Monatsblätter für Augenheilkunde*[3] he mentions 276 cataract extractions but makes no reference to complications. In this article he summarizes his views on the use of α-chymotrypsin: (1) The enzyme dissolves the zonule without damage to the vitreous. (2) No reactions are caused in the intraocular tissues that affect the postoperative course. (3) Enzymatic zonulysis (a) permits total cataract extraction independent of age, (b) obviates extracapsular extraction, (c) reduces vitreous loss, capsule tearing, reactions of the ciliary body, and retinal detachment, and (4) may make possible extraction of clear lenses for high myopia.

American ophthalmologists have been cautious and have formed a committee (Vail;[4] Troutman[5]) to investigate α-chymotrypsin.

Experimental work by Salmony,[6] Thorson and Leinfelder,[7] and Bedrossian[8] has failed to detect any pathological effects of the enzyme on intraocular tissues. But Bedrossian points out that no microscopic effect can be detected on the zonule either. Since the zonule is definitely altered by the enzyme, perhaps other structures are imperceptibly (to the microscope) altered.

Several British ophthalmologists have reported their experience in small series and have discussed complications. They, like the author, have had difficulty in deciding which complications might be due to the enzyme and which are incidental.

Cogan, Symonds and Gibbs[9] report a typical series of operative and postoperative complications in 122 cataract operations using α-chymotrypsin. They draw attention to three cases of postoperative iritis with hypopyon "with no obvious cause", though two of the patients were diabetics. They also had one case of severe hyphæma. They report normal wound healing. Similar complications are noted in this author's series.

Zorab[10] in 26 cases had one large vitreous hæmorrhage and one case of early Fuchs's dystrophy which became much worse after operation. In one of his cases, in which the patient was one year old, a successful intracapsular extraction without complications was performed with the use of the enzyme. In all cases wound healing was satisfactory.

Ainslie[11] in 32 cases had one case of hyphæma. In his cases, wound healing was satisfactory.

Orr[12] in 35 cases had one of postoperative iritis and one of unsatisfactory healing. This latter was a diabetic patient who suffered some vitreous loss.

Hill[13] reports a case of corneal vascularization which he thinks may have been due to the presence of hyaluronidase in the α-chymotrypsin. He refers to the work of Meyer and Chaffee,[14] who showed that hyaluronidase, when injected into the corneæ of cattle, permitted corneal vascularization and that this effect was prevented by inactivating hyaluronic acid ester.

No complications are reported by Remky[15] (68 cases), Rizzuti[16] (32 cases) or Malbran[17] (seven cases).

METHOD

Cataract extractions were performed in 32 consecutive unselected patients by the author or by the senior resident with the author assisting. When the eye was ready for lens extraction, 1 c.c. of α-chymotrypsin (British Drug Houses) in 1 in 5000 Ringer's solution was instilled under the iris at intervals of one minute. The posterior chamber was irrigated with saline three or three and a half minutes after the first α-chymotrypsin irrigation.

RESULTS

Fragile zonules were found in 29 eyes. Of these patients, two had sufficiently tough zonules in the other eye at a previous extraction to draw special comment by residents in their operation report. Tough zonules were found in two eyes of the four in patients under 60 years. One eye (patient aged 47) had a fragile zonule when the enzyme was left in the posterior chamber for a little longer—four minutes. Remky[15] states, "only possible error—attempting extraction with the enzyme not having acted long enough".

The zonule was resistant at 12 o'clock in one eye (patient aged 71) which had a previous iris inclusion. Perhaps the enzyme did not remain in contact with the zonule here.

In this series there was one instance of ruptured capsule as compared with one occurring in 32 consecutive cataract extractions performed before α-chymotrypsin was used. One vitreous loss occurred in the 32 cases in which the enzyme was used and one in the preceding 32 extractions.

Zorab[10] and Ainslie[11] refer to the difficulty in grasping the lens when it has become rounded after zonulysis. This difficulty was encountered in one of this series, but as the lens was black and particularly hard, it is unlikely that zonulysis was responsible.

Choroidal detachment was noted in two of this series whereas it was found in four of the 32 extractions before the enzyme was used.

Wound healing has been normal.

*From the Division of Ophthalmology, Department of Surgery, University of British Columbia, Vancouver.

COMPLICATIONS PERHAPS ATTRIBUTABLE TO THE ENZYME

Inflammation

An 81-year-old Negro (mild diabetic) was about to be discharged after a satisfactory operation and postoperative course when a hypopyon appeared on the sixth day. Despite all measures a severe enophthalmitis with dense membrane formation ensued. Conjunctival cultures were negative. A satisfactory cataract extraction had been performed on the other eye eight years before.

A 74-year-old man, who had previously had an unsatisfactory cataract extraction on the other eye elsewhere some years ago, had a satisfactory operation and postoperative course until the fifth day, when a small hypopyon was noted. The vitreous was cloudy and cultures of the conjunctiva were negative. The hypopyon resolved in four days with intensive antibiotic and steroid therapy. Strand opacities are still present in the vitreous after three months. The vision is 20/50 with good prospects of improving.

Three cases of mild iritis developed in the enzyme series compared with one in the pre-enzyme series. Each commenced two months after the extraction. The eyes have been congested with definite flare but keratitis punctata have been fine and infrequent. The vision has remained 20/20 in each but the iritis has been remarkably persistent (in one case lasting ten months). All three were in good physical condition and did not have diabetes. Their ages were 46, 58 and 65. The operations were uneventful except for the latter in which the lens delivered spontaneously and was followed by a small vitreous loss. Cogan[9] reports three cases of unexplained iritis and Orr[12] one case.

Hæmorrhage

A 46-year-old woman, after a satisfactory operation and a normal postoperative course, had a severe intraocular hæmorrhage on the sixth day. The anterior chamber cleared in two weeks but the vitreous hæmorrhage is not yet absorbed after five months though it has contracted, permitting 20/20 vision. Cogan[9] reports one case of severe hyphæma, as does Ainslie.[11]

COMPLICATIONS INCIDENTAL TO ENZYMATIC ZONULYSIS

The following have been discussed above: ruptured capsule (one case), difficulty in grasping capsule (one), vitreous loss (one), and choroidal detachment (two cases). Macular degeneration occurred in two, diabetic retinopathy in one, and superficial punctate keratitis in two—perhaps due to secondary virus infection encouraged by using cortisone drops too long postoperatively.

SUMMARY

The literature has been reviewed and the complications occurring in 32 consecutive unselected cataract extractions, using enzymatic zonulysis, have been discussed. The zonule was fragile in 29 and tough in three cases probably owing to the fact that the enzyme was not left in contact with the zonule long enough.

Three cases of late mild iritis may be attributable to the enzyme. One severe and one milder endophthalmitis and one severe hæmorrhage may also have had some connection with the use of *a*-chymotrypsin.

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RÉSUMÉ

Après un rappel de la littérature sur ce sujet l'auteur présente les faits saillants d'une série de 32 extractions de cataracte pratiquées avec zonulolyse enzymatique. La zonule fut trouvée fragile dans 29 cas et dure dans trois, probablement parceque l'enzyme n'avait pas agi assez longtemps. On a imputé trois cas d'iritis légère à ce nouveau procédé, et l'on prétend que deux cas d'endophtalmie, dont l'un était grave, ainsi qu'une forte hémorragie, peuvent y être rattachés.

MILK INTAKE

The answer to the mother's question: "How much milk should my child have a day?" should not be the statement of any quantity, but rather an inquiry into the child's diet as a whole. The milk intake should be considered in its relationship to intake of iron-supplying foods such as egg yolk, lean meat, vegetables, and fruits. Normally, the milk intake recommended can be "somewhere between two and four cups altogether," since many mothers think of the milk intake only as that drunk and forget that consumed in other foods. Most physicians or child health clinics will have printed literature to be given to mothers, or they will have posters illustrating these general principles on display in waiting rooms. It is recommended that any such visual educational material be phrased carefully to avoid such words as "must have", "at least", and "every day". This avoidance of specific regulations is a basic element in all child guidance and habit formation. It may be that a physician who inculcates in a mother a noncompulsive attitude towards milk or any other dietary item also may be building a better mother-child relationship in general.—C. A. Smith: *J. A. M. A.*, 172: 569, 1960.

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HEARTBURN*

ROBERT C. DICKSON, M.D., F.R.C.P.[C], F.A.C.P., *Halifax, N.S.*

THE DIAGNOSTIC value of any symptom is directly proportional to the knowledge of the mechanism of its production, and inversely proportional to the number of diseases in which it occurs. Some symptoms, like intermittent claudication or angina pectoris, have such specific meaning as to be, of themselves, virtually diagnostic. Others, such as heartburn, occurring as they do in a wide variety of conditions, appear to have so little diagnostic value as to be hardly worthy of consideration. However, if the mode of production of such a symptom is studied carefully and its clinical significance evaluated critically, it may prove more valuable than at first suspected. New methods of examination, often involving intricate and expensive equipment, have added very considerably to the physician's ability to reach an accurate diagnosis. Such techniques have a very definite value in their own right, but if full use is to be made of them, the information obtained must also provide a clearer understanding of common symptoms and signs. Thus the knowledge gained can be made available to all physicians who wish to improve their diagnostic skill, but who lack the equipment or training to use the new methods. It is from this point of view that this presentation on the symptom of heartburn has been prepared.

The clinical investigation of œsophageal disease has been facilitated by the introduction of the œsophagoscope equipped with a flexible obturator. On the experimental side, the development of the small electronic transducer, for the recording of pressure changes within the œsophagus, has provided a means of confirming and sometimes of adding to the observations of earlier studies which employed manometric and oncometric techniques.

Heartburn is defined as deep-seated burning discomfort situated behind the breastbone anywhere between the xiphoid and the upper border of the manubrium sterni. It must be distinguished from sour or acid regurgitation but, as will become apparent, this differentiation is difficult unless sour regurgitation is restricted to those instances where the regurgitated material reaches the mouth and can be tasted. Having so defined heartburn, it is now possible to consider its basic cause.

In his classic volume entitled "Digestive Tract Pain" published in 1938, Chester Jones[1] detailed the results of experiments in which he passed a balloon at the end of a tube to various levels in the gastro-intestinal tract. He then inflated it and recorded the character and location of the sensations produced. These experiments have been repeated, and in some instances elaborated, by others, but the basic interpretations that Jones made have not been altered. With the balloon at the lower end of the œsophagus just above the diaphragmatic hiatus, pain was produced which was described as burning by the majority of the subjects so studied, but by a few was described as dull and gripping rather than burning. In a few instances the pain radiated upward in wave-like fashion as high as the throat. It is easy to understand how in patients with such radiation, heartburn can be confused with sour regurgitation and why it is imperative that the latter term be limited to those instances in which material actually reaches the mouth and can be tasted. Jones's next step was to inject various fluids into the lower œsophagus and to compare their effect. He used tenth normal hydrochloric acid, tenth normal sodium hydroxide, warm water, cold water, gastric juice and barium emulsion. He found that the character of the fluid did not matter. All produced the symptom if the injection was sufficiently rapid. Fluoroscopy with barium emulsion showed increased tone in the area, and those patients in whom the heartburn radiated upward had reverse peristalsis. Jones concluded that heartburn was due to increased pressure on nerve endings within the wall of the œsophagus, brought about by increased tone or spasm or by stretching—but it is important to note that his comparison of the effects of various fluids was based on short experiments.

In clinical medicine the physician encounters many examples of distended viscera which are painless. In organs such as the urinary bladder where pressure can be measured easily, it has been shown that distension produces pain only when there is a rise in pressure indicative of increased tone. It seems reasonable to conclude that the painful pressure on nerve endings results from increased tone, whether this occurs in the distended organ or in the contracted one.

It would be a happy situation if we could leave heartburn at this point and consider it as always due to increased tone or spasm of muscle. However, recent work has made it essential to review again the effect of acid on an inflamed mucosa. Turning for a moment to that most controversial of medical subjects, the cause of pain in peptic ulcer, it is apparent that the old argument has not been resolved as to whether the pain is due to increased tone or spasm in all instances, or whether acid pepsin acting on the inflamed area of ulceration can, of itself, produce pain. In an editorial comment the case for increased tone was ably presented by Bloomfield,[2] while that for the effect of acid on mucosa sensitized by inflammation was equally well expounded by Walter Palmer.[3] To this observer, at this time, it appears that sensory nerve endings near the inflamed mucosa in the region of a peptic ulcer are sensitive to changes in tone not appreciated by the healthy stomach or duodenum, and are also sensitive to other stimuli such as that produced by sufficiently prolonged contact with hydrochloric acid. It is particularly hard to

*From the Department of Medicine, Dalhousie University, and the Victoria General and Camp Hill Hospitals, Halifax, N.S.

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deny the conclusion of Palmer, based on simultaneous radiographic and manometric studies, that pain could be induced in patients with peptic ulcer by hydrochloric acid without increased tone or spasm of muscle detectable by these methods. Whether or not, under such circumstances, spasm occurred in the immediate region of the ulcer, was too localized to be detected by the methods used, and was the ultimate cause of the pain is beside the point. It is clear that acid acting on inflamed mucosa was the precipitating cause.

To return to the œsophagus, Bernstein and Baker[4] have shown that in people with œsophagitis a slow drip of tenth normal hydrochloric acid continued for periods up to half an hour produced heartburn, whereas in people without œsophagitis no discomfort was produced. They conclude, as does Palmer, that the effect of hydrochloric acid on an inflamed mucosa is to produce pain. They, too, claim that such pain is not accompanied by spasm which can be detected by manometric studies. In Halifax a few patients have been so tested with findings which support those of Bernstein and Baker.

To summarize, the evidence at this time indicates that œsophageal pain or heartburn can be produced by increased tone or spasm, or by irritation of an inflamed mucosa by sufficiently long exposure to hydrochloric acid. It should be noted that while the work referred to above is recent, as long ago as 1884, Reichman[5] reported that small sponges placed for a period of time in the lower œsophagus absorbed fluid of acid reaction in patients who experienced heartburn.

Heartburn can be produced by local irritation of the œsophagus, by increased tone resulting from reflex stimulation initiated by disease in distant organs, and possibly also by emotional causes. It is described by some patients as tight, dull, or gripping, rather than burning. In any patient, if the intensity or duration of the stimulus is increased, it is described as pain.

Trauma, as from swallowed foreign bodies, infection, and the effect of escharotics, all may cause acute œsophagitis and hence heartburn. These will not be discussed. Subacute or recurrent œsophagitis may be due to peptic digestion, trauma from tubes, or stasis. Of these, peptic or reflux œsophagitis is the most common, much more common than was generally appreciated before the introduction of the flexible œsophagoscope and its more frequent use by physicians.

That gastric juice can cause inflammation and erosion of the œsophageal mucosa has been clearly shown by Wangensteen's[6] experiments in which he caused gastric juice to drip into the œsophagus of the anæsthetized cat for a period of two hours. This always produced acute inflammatory changes—the changes being more marked when the gastric juice came from patients with duodenal ulcer. It is apparent, then, that at least two factors are concerned in the production of reflux œsophagitis—the ease with which gastric juice can enter the lower œsophagus, and the peptic activity of the gastric juice.

FACTORS IN THE PREVENTION OF REFLUX

Throughout the animal kingdom the mechanism for the prevention of œsophageal reflux varies. In some animals no intrinsic anatomical sphincter is demonstrable. In others, such as the rabbit which cannot vomit, and the bat accustomed to hanging head down throughout the day, well-developed anatomical sphincters have been identified. The absence of an anatomical intrinsic sphincter in man has led to controversy as to what prevents reflux. At best, a mechanism which will permit vomiting and the easy eructation of gas must be an imperfect one. Recent studies using a variety of methods have largely clarified the situation and permit evaluation of the various theories which have been suggested.

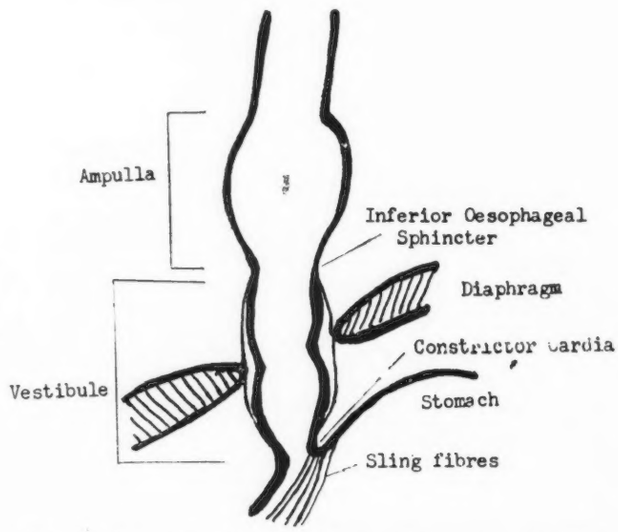

Fig. 1.—Schematic diagram of œsophagogastric junction adapted from Lerche.

On the basis of radiological studies, Lerche[7] considered that there was an intrinsic lower œsophageal sphincter at the upper end of the vestibule and a further sphincter at the cardia provided by the fibres of the oblique muscle coat of the stomach which, in the region of the cardia, form a sling about the œsophagogastric junction (Fig. 1). Fyke[8] and co-workers, using minute electronic transducers, were able to demonstrate a zone extending from 1-2 cm. below the diaphragmatic hiatus to 1-2 cm. above it, where the resting intraluminal pressure was higher than that of the œsophagus above it, or the stomach below. This zone corresponds to the vestibule described by Lerche, and to the zone described by Sanchez, Kramer and Ingelfinger[9] as having a characteristic motor function separate from, but co-ordinated with, that of the remainder of the œsophagus. They were able to show, by simultaneous radiographic observation and pressure recordings obtained by using electronic transducers, that the œsophageal peristaltic wave was not

propagated into the vestibule. On the approach of the wave the vestibule relaxed, permitting the œsophageal contents to be emptied into it by the progressing high pressure gradient between the lower œsophagus and the vestibule. Vestibular contraction then followed with higher pressures in the part above the diaphragm than in that below and emptying of the vestibular contents into the stomach. This mechanism causes the arrest of swallowed fluid at the lower end of the œsophagus pending the arrival of the next peristaltic wave. The studies of Ingelfinger and his group have been confirmed by Hightower[10] and leave little doubt that the vestibule acts as a unit. In addition to its function in deglutition, the high resting tone of this segment must be considered in the mechanism for prevention of reflux. Peristaltic activity and hence vestibular activity are dependent upon the integrity of the intrinsic nerve supply based on the myenteric plexuses of Auerbach and at least one intact vagus nerve. In Table I are noted the chief mechanisms to which the prevention of reflux have been attributed.

TABLE I.—SUGGESTED MECHANISMS FOR PREVENTION OF REFLUX

Intrinsic sphincter
Pinchcock action of diaphragm
Flap valve
Oblique entry of œsophagus
Liver tunnel
Sphincter cardia
Occluding mucosal folds

The pinchcock action of the diaphragm has attracted the attention of radiologists. Some note that, during inspiration, emptying of the barium-filled œsophagus may be interrupted. Others report that respiration does not affect deglutition in any way, while still others state that emptying of the œsophagus is accomplished better during inspiration. The pinchcock effect is due to the arrangement of the crural fibres, particularly those of the right crus. Leigh Collis[11] has given a detailed description of the crura and has indicated the anatomical variations which are found. That the diaphragm may exert an effect was well shown by the study of a patient with scleroderma of the œsophagus at the Victoria General Hospital. The absence of peristalsis, owing to the intrinsic disease of the œsophageal wall, eliminated this factor. With the patient recumbent, barium remained in the œsophagus for periods up to half an hour. In the upright position, the effect of breathing was very apparent to the radiologist on fluoroscopy, and the barium was seen to leave the œsophagus in expiration, but to be held up during inspiration. In some people the crura evidently delay the emptying of the œsophagus during inspiration.

However, because the diaphragmatic crura interfere with emptying of the œsophagus they need not also have the effect of preventing reflux. Paralysis of either diaphragm is not followed by unusual reflux nor, indeed, is paralysis of both diaphragms in patients with poliomyelitis of necessity followed by evidence of reflux. Finally, the act of vomiting, the most striking example of reflux, involves fixation of the diaphragm in the inspiratory position. The pinchcock action of the diaphragm therefore is of no value in the prevention of reflux.

The one-way flap valve theory is an attractive one which, unfortunately, is not borne out by anatomical studies. The appearance of the œsophageal hiatus from below, as a rosette of mucosal folds rather than a slit, does not justify the assumption that a flap valve is a factor in the prevention of reflux. However, the oblique entry of the œsophagus into the stomach provides an arrangement for preventing a rising pressure in the stomach from acting directly against the œsophageal orifice, and may make possible the application of pressure on the abdominal œophagus between the distended fundus of the stomach and the liver.

The sphincter cardia, described by Lerche, is provided in large part by fibres of the oblique muscle coat of the stomach arranged in a sling fashion about the œsophago-gastric junction; it has not been shown to be essential. These fibres may possibly be of value in helping to maintain the acute angle of junction of the œsophagus with the stomach.

The theory of occluding mucosal folds at the cardia has been studied recently by G. S. Muller Botha[12] as part of a more general consideration of the closing mechanism between the stomach and œsophagus. In his Hunterian lecture, delivered before the Royal College of Surgeons of England in December 1958, Botha presented his views based in part on comparative anatomical studies in several species. He points out that in the tortoise, which has no diaphragm, no acute angle of junction and no anatomical sphincter, these mucosal folds are the only remaining mechanism apart from a physiological sphincter that could prevent forcible ejection of gastric content when the stomach contracts. In the rabbit and bat there are well-developed anatomical sphincters and a very clear rosette of mucosal folds at the cardia. Botha stresses the importance of the muscularis mucosa, well developed at the lower, but absent at the upper end of the œsophagus, in forming the mucosal folds into a rosette. The importance of such folds is difficult to determine, but it seems unlikely that they do more than provide a plug, the position of which must be maintained by the vestibular muscle. Allison[13] comments that "Anyone old enough to have actually ridden in a [horse-drawn] cab knows that a mucosa-lined tube big enough to allow passage of a mass will, when closing, form a rosette." This is entertaining, but does not preclude the mucosal folds from contributing to the prevention of reflux.

In summary, the factors concerned with the prevention of reflux appear to be as follows: Most important is the intrinsic sphincteric mechanism consisting of mucosal folds, drawn into rosette

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arrangement by the well-developed muscularis mucosa found in this region, but maintained there by the inherent tone of the vestibule. The existence of separate cardiac and inferior œsophageal sphincters can be questioned. Rather, these appear to represent the upper and lower limits of the vestibule acting as a unit. A further contribution to the sphincteric mechanism is the maintenance of an acute angle of junction between œsophagus and stomach at a point below the diaphragm. The factors concerned in this fixation are the left gastric artery, the phrenico-œsophageal ligament, the diaphragmatic crura, and perhaps the sling fibres at the cardia.

STUDY OF PATIENTS WITH HEARTBURN

With the foregoing valuable anatomical and physiological information in mind, it is of some interest to consider what can be learned from the study of patients with heartburn. Without very special equipment it is difficult to determine directly the integrity of the intrinsic sphincteric mechanism of the vestibule, but consideration of other factors contributing to the prevention of reflux provides indirect evidence of its importance.

The newborn infant regurgitates food easily and often. Sometimes this normal state of affairs persists longer than is usual and leads to radiological examination. Some such children are found to have a sliding type of œsophageal hiatus hernia, as emphasized in a recent excellent review by Swyer.[14] In others the essential findings are an obtuse angle of junction between the œsophagus and stomach, free reflux of barium from stomach to œsophagus, and a patulous lower œsophageal segment. This condition has been termed chalasia of the cardia (Fig. 2). Most of these children by the age of two years have ceased to regurgitate food. Two possible explanations may be considered. Either an intrinsic sphincteric mechanism, rarely effective at birth, has taken longer than usual to develop, or the relation between stomach and diaphragm has changed so that a more acute angle of junction has been formed. The former seems to be more likely.

In adults such an obtuse angle may or may not be associated with œsophagitis and heartburn, but apart from the sliding type of hiatal hernia it is the anatomical abnormality most often associated with them. It is easy to understand how an obtuse angle of junction permits pressure produced by the contracting stomach to be exerted more directly on the aperture of the cardia than where the more usual oblique entry obtains. Nevertheless, in some an efficient intrinsic sphincter is apparently still able to provide a sufficient barrier against reflux to protect the œsophagus from peptic œsophagitis. The potency of the peptic factor in gastric juice must also be considered. In one patient with an obtuse angle of junction and a history of frequent sour regurgitation, it seemed to explain the absence of œsophagitis and heartburn. This patient had

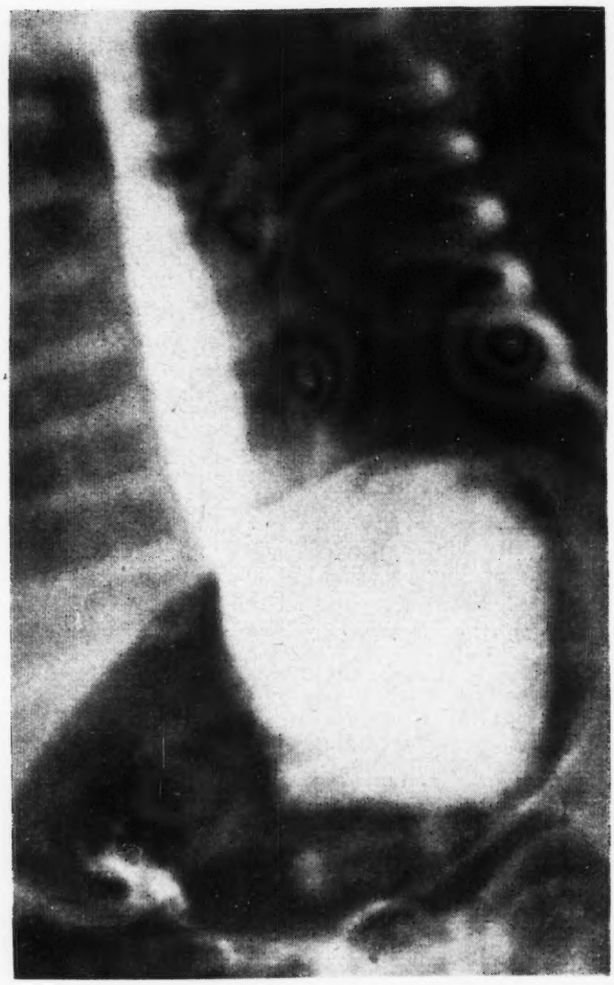

Fig. 2.—Chalasia of cardia.

atrophic gastritis with no free hydrochloric acid in the gastric juice and a very low excretion of uropepsin. There was no œsophagoscopic evidence of œsophagitis.

A further opportunity to study the effect of the loss of the acute angle of junction of œsophagus and stomach is provided by patients with the sliding type of œsophageal hiatus hernia. Here the œsophagus enters directly into the stomach at a point above the diaphragm and the arrangement provides a funnel to direct intragastric pressure directly against the œsophageal orifice. Yet it is well known that although many patients with œsophagitis have a sliding hiatal hernia, many other patients with a sliding hiatal hernia have no symptoms to suggest its presence.

A recent case well illustrates this point. The patient, a man of 50 years, was admitted because of very severe upper gastro-intestinal hæmorrhage which fortunately ceased while the patient was under supportive treatment. This patient had never experienced heartburn or other discomfort which could be construed to be of œsophageal origin. Radiological examination demonstrated an œsophageal hiatus hernia and an active duodenal ulcer (Fig. 3). Œsophagoscopy revealed an entirely

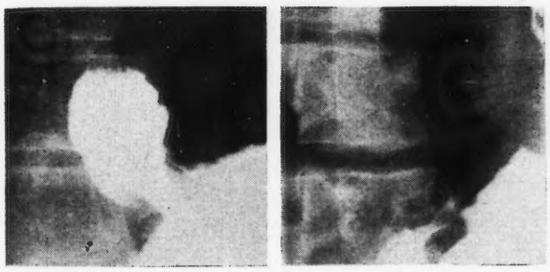

Fig. 3.—Œsophageal hiatus hernia and duodenal ulcer. Left—sliding hernia. Note absence of reflux above the hernia. Right—crater of duodenal ulcer.

normal œsophageal mucosa. In this patient the intrinsic sphincteric mechanism was able to protect the œsophagus from the effect of gastric juice capable of producing duodenal ulcer in spite of the loss of the acute angle at the œsophagogastric junction and the presence of a sliding œsophageal hiatus hernia.

Repair of an œsophageal hiatus hernia is sometimes followed by healing of œsophagitis and relief of heartburn. No operation has yet been devised which improves the function of the intrinsic sphincter. It seems likely that alteration of the œsophagogastric junction to produce an acute angle is the most important contribution that surgery can provide. Fig. 4 shows failure of an operation to alter the angle of entry, and in this case there was no improvement of œsophagitis or heartburn.

Fig. 4.—Hiatal hernia before and after repair showing failure of operation to alter the angle at the œsophagogastric junction.

The intrinsic sphincter is, then, clinically supported as the most important factor in preventing abnormal reflux and peptic œsophagitis.

Recumbency and increase in intra-abdominal pressure promote reflux. Heartburn may first appear after a gain in weight with consequent increase in intra-abdominal and hence intra-gastric pressure. It is usually more marked at night or after a large meal. A patient was seen recently because of persistent duodenal ulcer symptoms due to a moderate degree of pyloric obstruction. He first experienced heartburn after the symptoms of pyloric obstruction began. Œsophagoscopy confirmed a diagnosis of œsophagitis. A sphincter competent for ordinary purposes therefore may be inadequate when the intragastric pressure is high. Another example of this was provided by a little woman seen on ward rounds in St. John's, Newfoundland. She had been admitted with ascites due to peritoneal implants of ovarian malignancy. Her chief complaint was heartburn which she stated she had experienced during the latter months of each of her nine pregnancies, but never in the 20 years after the birth of her last child, until her abdomen began to swell with ascites.

Heartburn of pregnancy occurs most commonly in the later months. The increasing intra-abdominal pressure is perhaps the reason. It would be unwise to accept this explanation without examining the subject more carefully. Heartburn sometimes begins early in pregnancy and in such instances is likely to be persistent and progressively more severe as the pregnancy proceeds.

In Fig. 5 is a radiograph of the œsophagogastric junction in a young woman in the second month of her second pregnancy. She had suffered from severe heartburn throughout her first pregnancy and again early in this one. The œsophagogastric angle is acute and placed well below the diaphragm. At two months, enlargement of the uterus

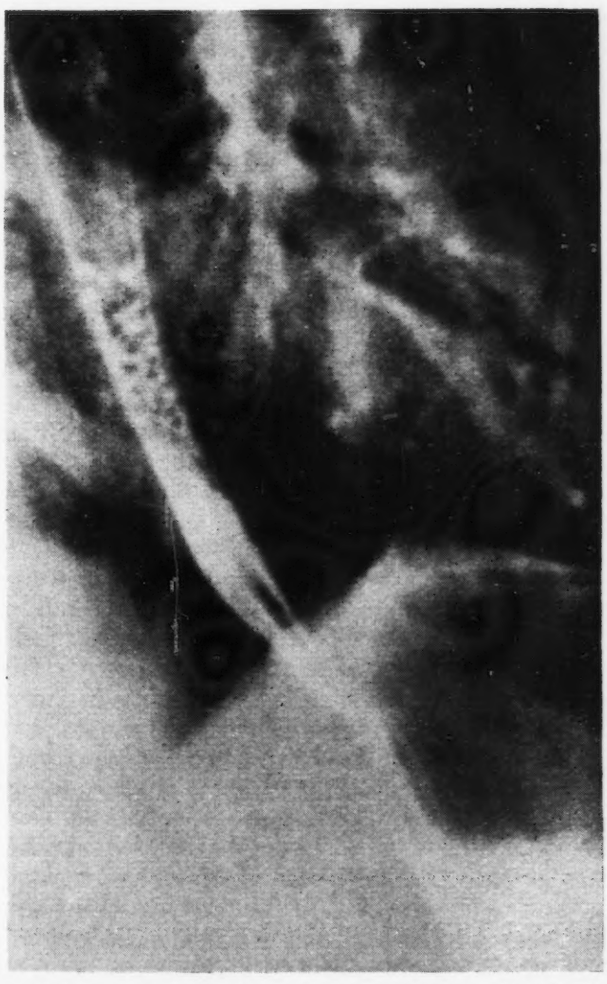

Fig. 5.—Acute angle of junction of œsophagus with stomach in a patient with severe heartburn of pregnancy.

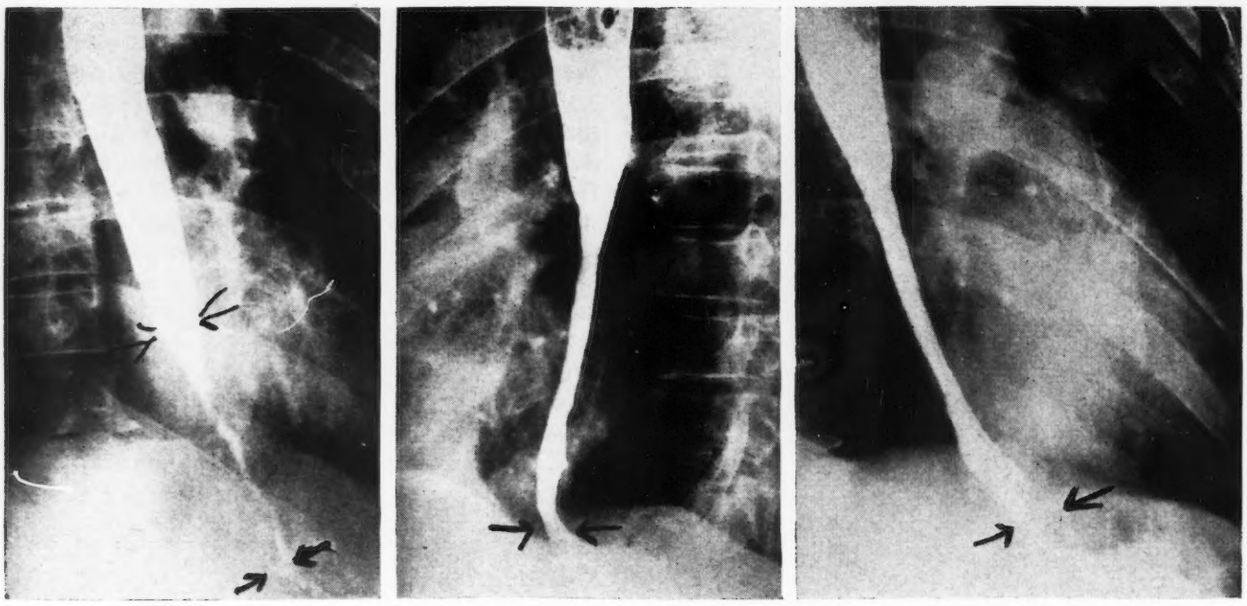

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Fig. 6.—Stricture following intubation. Left—six weeks after intubation. Centre—six months after intubation. Right—10 months after intubation showing sliding hernia.

could hardly be a serious factor in causing reflux. Œsophagoscopy revealed acute œsophagitis. In this instance, neither increased intra-abdominal pressure nor loss of the acute angle of junction of œsophagus with stomach explained the inflammation. The intrinsic sphincter and the potency of gastric juice remained to be considered. At the œsophagoscopic examination, although the angulation at the hiatus was definite and a rosette was seen, some reflux was observed. Without very careful studies of pressures in the vestibule it would be impossible to assess the integrity of the internal sphincter. Yet the knowledge that reduction in tone of the muscle of the ureters and stomach occurs during pregnancy indicates the possibility of a similar reduction of tone in the vestibule.

A study of the effect of pregnancy on the potency of gastric juice has recently been started at Dalhousie University, using the output of uropepsin as an index of peptic activity of gastric juice. Janowitz, Levy and Hollander[15] have demonstrated that the output of uropepsin in the urine is a constant fraction of the pepsinogen secretion by the chief cells and hence reflects their activity. Tonning and Brown,[16] working at Dalhousie with the aid of a grant from the National Research Council, have confirmed the observations of Gray[17] and his co-workers that hyperfunction of the anterior pituitary or adrenal cortex is associated with high outputs of uropepsin, and hypofunction of these organs with low outputs. Similarly, the administration of ACTH or cortisone causes an increase in the output of uropepsin.

It has long been known that hypertrophy of the adrenal cortex occurs during pregnancy, and Venning[18] has reported an increased output of certain of the adrenal steroids including the glycogenic corticoids. Increased blood levels of adrenocorticosteroids during pregnancy were reported by Gemzell,[19] and a rise of uropepsin during pregnancy might, therefore, be expected. However, Laidlaw,[20] who has also found progressively rising blood levels of 17-hydroxycorticoids in pregnancy, points out that the total amount of excretion does not rise, and questions the activity of the hormones in view of the absence of signs of Cushing's syndrome in pregnant women. The remissions that occur during pregnancy in some cases of rheumatoid arthritis, asthma and ulcerative colitis, suggest that in some instances adrenocortical activity is increased. Further, the occurrence of striæ extending to the upper thighs, reduced glucose tolerance, and occasionally mild hirsutism suggest that in some pregnant women evidence of mild Cushing's syndrome is present. Some mechanism to offset the results of higher blood levels of adrenocorticoids would seem to be operative in pregnant women, but its efficiency may vary in different individuals.

These observations indicate the need for a study of uropepsin excretion in pregnancy and this has been commenced at Dalhousie with a view to determining whether there is any change in its excretion and whether any increase that occurs is related to the development of heartburn.

Œsophagitis and stricture have been observed to develop in patients who have had a tube left in the œsophagus for several days. As an example of this serious complication, a 62-year-old shipwright, who had suffered for many years from duodenal ulcer, underwent partial gastrectomy in August 1956. Heartburn was not one of the symptoms of which this patient complained before operation.

Postoperatively, a Levine tube was left in his stomach for five days during which time he complained continuously and bitterly of burning pain at the lower end of his sternum. After removal of the tube the patient still complained of heartburn, and about the time he left hospital was beginning to note some dysphagia. He was brought back to hospital a month later with severe dysphagia and was found to have a stricture as seen on the left in Fig. 6. Before operation this patient had never had œsophageal symptoms, either dysphagia or heartburn, that might have suggested reflux. Furthermore, he had had repeated radiographic examinations of his upper gastro-intestinal tract, which included fluoroscopy of the œsophagus. Unfortunately, no plates before this operation showed the œsophagus, but the radiologist who examined him repeatedly had no doubt at all about its having presented a normal appearance.

The mechanism of such an œsophagitis is perhaps open to some debate, but it is interesting to note that this patient, in spite of the gastrectomy, still had free hydrochloric acid in the fasting gastric juice. Reflux œsophagitis may have been brought about by the tube's rendering the intrinsic sphincter incompetent. This patient has been treated by periodic dilatation of the œsophagus and administration of anticholinergic drugs, and has carried on very well. He has regained some of the weight lost at the time of his operation and just afterwards. He still complains of heartburn. Note now the centre picture in Fig. 6. At first glance it might seem that the stricture has extended upward. Another explanation for the appearance is that the œsophagus has been shortened. If the length of the narrowed portion of the œsophagus is compared in the two pictures, it is seen to be the same. In the right-hand picture of Fig. 7 true shortening is confirmed and the beginning of a sliding type of œsophageal hiatus hernia may be seen. This case also illustrates the role that œsophagitis may play in the production of such hernias. Granted a faulty fixation of the stomach below the diaphragm, an obtuse angle of junction as in chalasia, and an incompetent intrinsic sphincter, œsophagitis followed by shortening of the œsophagus can develop.

It is easy to understand how retention of food behind an obstruction caused by cardiospasm, stricture, or carcinoma can result in infection, inflammation and heartburn. It is of some importance to consider what part such an event plays in the natural history of cardiospasm or, as it is more properly termed, achalasia. The careful studies of Kramer, Ingelfinger and Atkinson[21] and others have clearly shown that synchronized peristaltic waves are not seen in achalasia, and that the muscle of the œsophagus responds to drugs in an exaggerated manner in accordance with Cannon's law. The vestibule does not relax, possibly because of the absence of the peristaltic wave, but

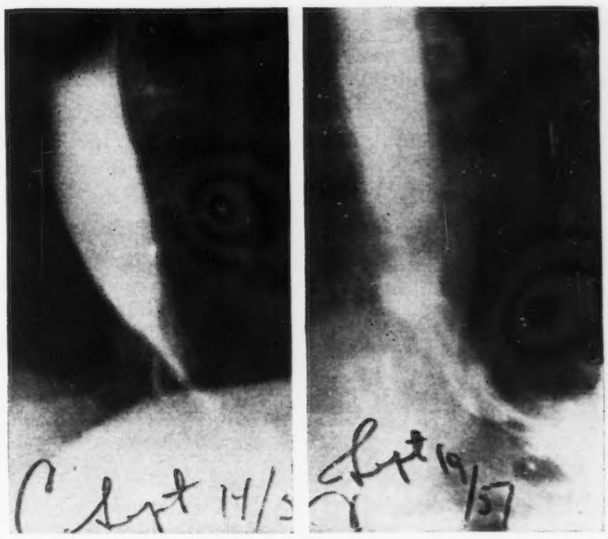

Fig. 7.—Reflex spasm of lower œsophagus from duodenal ulcer. Left—before treatment. Right—after treatment.

no spasm can be demonstrated in this area. The pathological basis for this derangement is degeneration of the parasympathetic ganglion cells of Auerbach's plexus.

Those who have followed the natural history of this disorder will know that a patient with achalasia may carry on for long periods with little or no difficulty, then often quite suddenly be unable to swallow at all. Such exacerbations are accompanied by heartburn. If the œsophagus is washed out and œsophagoscopic examination conducted, the distal portion is found acutely inflamed. The next case illustrates this feature very well.

A man of 38 years was admitted to Camp Hill Hospital, D.V.A., because of severe heartburn and dysphagia of one week's duration. At a previous admission a diagnosis of achalasia had been made, based on history and radiographic findings. On this admission the œsophagoscopy revealed such intense œsophagitis that the examiner questioned the diagnosis and suggested that perhaps this was a case of reflux œsophagitis with stricture. However, after dilatation with a Hurst mercury-filled tube, carried out at first in hospital and later at home by the patient, re-examination revealed an entirely normal mucosa. The patient has subsequently carried on for three years without difficulty.

When such a patient is first treated by dilatation with a Hurst mercury-filled tube, a definite sense of resistance is encountered. This is one of the observations that have led to the belief that there is actual spasm of the vestibule. Such is indeed the case, but it is a secondary effect due to inflammation. Later, when the œsophagitis has subsided, the tube is passed without encountering any sense of resistance whatever. The practical implications of these observations are of importance in the treatment of achalasia. If the patient is taught to pass a tube each evening, the œsophagus will be cleared of residue and the likelihood of stasis œsophagitis lessened. On the other hand, treatment of this

condition by elimination of the sphincteric action of the vestibule by anastomotic operations, muscle-incising operations of the Heller type, or fracture of the muscle fibres by use of the hydrostatic bag have the disadvantage of also eliminating the most important factor in the prevention of reflux. The serious œsophagitis that develops in some patients so treated, points to the advisability of avoiding such methods if at all possible, particularly in those with evidence of a tendency to produce peptic ulcer.

Heartburn of reflex origin is most commonly due to peptic ulcer. A case illustrating this was recently referred to the Victoria General Hospital with a tentative diagnosis of carcinoma of the œsophagus.

The patient, a 77-year-old man, gave a history of heartburn occurring two hours after meals at intervals over the previous three years. Complete remissions lasting several months had occurred. Stooping and recumbency did not affect the symptom. It was relieved by milk and baking soda. It did not occur at night. A radiograph (Fig. 7, left) taken before admission revealed distinct narrowing of the lower œsophagus persistent throughout the examination. Œsophagoscopy performed under anæsthesia revealed an entirely normal œsophagus. The instrument was passed easily into the stomach. After a week's treatment of rest and bland diet, during which period the patient's symptoms subsided, repeat radiological examination (Fig. 7 right) demonstrated a normal œsophagus and a duodenal ulcer.

Heartburn is often described as a symptom of gall-bladder disease and may occur in association with attacks of biliary colic or acute cholecystitis. It is considered by some to be a feature of that most invidious of medical myths, cholecystic indigestion. In patients who have gall stones that are not giving rise to acute attacks of cystic or common bile duct obstruction, heartburn should not be attributed to the gall stones—rather, its proper cause should be sought and treated. If under such circumstances the gall bladder is removed, the heartburn will persist.

Emotion is known to cause increased tone or spasm in the stomach, duodenum, small intestine and colon. It is entirely likely that the same is true of the œsophagus. However, as an isolated symptom heartburn appears to be very rarely, indeed, of emotional origin. The occurrence of heartburn in a patient experiencing a period of emotional stress could mean that emotion caused or aggravated the heartburn, that the heartburn caused or aggravated the emotional upset, that both were due to a third factor, or that the two were unrelated causally one to the other. Before this symptom is termed functional, a positive diagnosis of neurosis must be made and other causes of heartburn excluded.

The final case illustrates the relationship between heartburn and cardiac ischæmic pain. Kramer found that many patients with angina pectoris could not distinguish between this pain and that produced by a balloon distended in the œsophagus. Some of his patients had electrocardiographic changes, but some had not.

A patient seen not long ago gave a history of rather rapid increase in weight over the preceding 12 months. About six weeks before the episode which caused him to seek medical advice, he noted the onset of frequent regurgitation of sour material into his mouth. Such regurgitation became associated with heartburn which became worse until one evening he was wakened from sleep with the feeling that a red-hot poker had been thrust down his throat. When seen by his physician he was writhing about in bed. Blood pressure was 120/90 mm. Hg; temperature, white blood cell count and sedimentation rate proved to be normal. The first electrocardiogram taken after the pain had been relieved by morphine was within normal limits. The second one taken during an attack of pain had findings indicative of posterior myocardial ischæmia. Treatment with alkalis, diet and, most important, reduction in weight, was followed by relief from heartburn and sour regurgitation and return of the electrocardiogram to normal. This man had a strong family history of atherosclerosis. It was felt that he had a degree of atherosclerosis of his coronary vessels insufficient to give evidence of ischæmia under ordinary conditions, but that severe heartburn caused by reflux œsophagitis confirmed by œsophagoscopy, had reflexly caused an increase in tone of the diseased coronary vessels sufficient to bring on ischæmia.

In conclusion, it may be said that the proper interpretation of the symptom, heartburn, makes possible more accurate diagnosis in many instances and serves as a guide to proper treatment in others. The attempts at interpretation may stimulate curiosity about more obscure causes and so perhaps contribute to medical advance.

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RÉSUMÉ

La valeur diagnostique d'un symptôme est directement proportionnelle à la connaissance que nous avons de son mécanisme de production et inversement proportionnelle au nombre de maladies dans lequel on le trouve. Les "maux de cœur" ou "brûlements d'estomac" sont définis comme étant une sensation de brûlement profond localisé derrière le sternum entre la poignée et l'appendice xyphoïde. On les retrouve dans une foule de maladies si bien qu'on pourrait à première vue considérer la valeur diagnostique de ce symptôme comme très limitée. L'expérience a prouvé cependant qu'on peut en tirer des renseignements précieux.

L'inflation d'un ballon à l'extrémité inférieure de l'œsophage cause chez la majorité des sujets une sensation de brûlement. Jones conclut de cette expérience que toute augmentation de pression exercée sur les terminaisons nerveuses de la paroi de l'œsophage peut causer cette sensation. Il semble d'autre part qu'une muqueuse enflammée exposée à l'action de l'acide chlorhydrique peut aussi donner lieu à ce malaise. Les traumatismes comme il en résulte de l'ingestion de corps étrangers, d'infections et d'escarrotiques peuvent causer de l'œsophagite et des brûlements d'estomac. Le mécanisme de reflux du suc gastrique dans l'œsophage inférieur varie selon les espèces animales. Quelques unes possèdent un sphincter bien établi comme le lapin ou la chauve-souris, d'autres n'en ont qu'une ébauche. L'homme appartient à cette dernière catégorie. Il existe une région de 1 à 2 cm. de long où la pression à l'intérieur de la lumière au repos est plus élevée que celle du reste de l'œsophage ou de l'estomac. Cette zone, appellée *vestibule* par Lerche, ne transmet pas les ondes péristaltiques. Au contraire à l'approche d'une d'entre elles on observe un relâchement du vestibule qui permet au bol alimentaire de descendre sans obstruction. L'activité péristaltique et vestibulaire dépend de l'intégrité de l'innervation des plexus myentériques d'Auerbach et d'au moins un pneumogastrique.

Les radiologistes se sont arrêtés à l'étude du diaphragme qui dans ces circonstances agit comme une pince d'arrêt. Il est évident que chez certains sujets les piliers du diaphragme retardent l'évacuation de l'œsophage pendant l'inspiration, cependant leur influence ne semble pas s'étendre beaucoup au delà de cette action. Dans les vomissements le diaphragme est fixé en position inspiratoire. La théorie de la valve à clapet, si attrayante soit-elle, n'est pas appuyée par des constatations anatomiques. Les fibres de la couche musculaire oblique de l'estomac qui dans une large part constituent le sphincter du cardia ne sont pas essentielles à son bon fonctionnement. L'angle aigu que forme l'œsophage et l'estomac contribue sans doute au mécanisme sphinctérien. La régurgitation est fréquente chez les tout jeunes enfants; elle cesse vers l'âge de deux ans ou avant, ce qui semblerait indiquer le développement d'un mécanisme sphinctérien intrinsèque rarement agissant à la naissance. La chirurgie en général n'a pas grand'chose à offrir dans l'amélioration de la fonction du sphincter intrinsèque; l'intervention la plus pratique est encore celle qui rétablit l'acuité de l'angle œsophago-gastrique devenu obtus.

La position horizontale et l'augmentation de la pression intra-abdominale favorisent le reflux du suc gastrique dans l'œsophage. Les brûlements d'estomac peuvent donc apparaître après un gain pondéral et ils se manifestent surtout la nuit ou après un repas copieux. On les observe aussi vers la fin de la grossesse ou dans les cas d'ascite. Au cours de la grossesse les régurgitations acides peuvent aussi être causées par l'abaissement du pH gastrique, secondaire à une hypertrophie du cortex surrénal. Les exacerbations que l'on note dans l'achalasie sont accompagnées de brûlements d'estomac. Ces périodes coïncideraient avec une inflammation aiguë de la partie distale de l'œsophage. Dans ces cas la dilatation par un tube à mercure de Hurst a pour effet de faciliter l'évacuation des débris alimentaires qui sont accumulés en amont du spasme et de permettre à l'inflammation de s'apaiser. Les brûlements d'estomac d'origine réflexe sont communément causés par un ulcère peptique, mais ils ne semblent pas être impliqués dans les coliques hépatiques ou la cholécystite aiguë.

CASE REPORT

LIPOSARCOMA OF THE BREAST
CASE REPORT AND REVIEW OF LITERATURE

J. K. McGREGOR, M.D., C.M.,* *Buffalo, N.Y.*

LIPOSARCOMA of the breast is a rare tumour derived from lipoblasts and is usually highly undifferentiated. The cells contain a variable quantity of vacuolated fat. These tumours occur most frequently in the retroperitoneal fat,[1, 2] and in the extremities.[3] The histological features of liposarcoma were first described by Virchow (Seids[4]) in 1857, although earlier reference to such a tumour was made by Morgagne of a patient who had metastatic lesions in the mediastinum, lungs and brain.[1]

Approximately 3% of all malignant breast tumours are sarcomas. Of these approximately 0.3% are liposarcomas. Cases have been reported in both sexes.[5, 6] It occurs most frequently in the middle-aged or elderly, but has been reported in patients between 25 and 76 years of age.

*From the Department of Surgery, The Buffalo General Hospital, Buffalo, New York, U.S.A.

CLINICAL APPEARANCE

Patients with liposarcoma of the breast commonly present with a slowly enlarging mass that has been present for more than one year. The lesion is generally a non-tender, solitary mass, although as many as ten discrete nodules have been described in one breast.[5] These tumours are rarely fixed to the deep fascia or overlying skin, and consequently are freely movable in the surrounding tissue. They may show different rates of growth, the same tumour growing rapidly at one time and slowly at another. Liposarcomas vary markedly in their consistency to palpation, depending on the amount of fibrous and myxomatous tissue present. Most frequently they are firm, circumscribed, bulky tumours with a well-defined but delicate capsule. Local recurrence is common after inadequate resection. A recurrent tumour frequently invades the skin and pectoral muscles. Unlike most sarcomas of the breast, axillary

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metastasis occurs occasionally.[7] The most common method of dissemination is via the blood stream, metastases often occurring in the lungs, mediastinum, and joints. Death in these patients is frequently due to pulmonary metastases.[8]

PATHOLOGY

Liposarcomas are generally well encapsulated and seem to shell out with little difficulty. The tumour mass, however, may not be uniform in shape as clinically suspected, but rather may have pseudopodia-like projections which are covered by reflections of the thin connective tissue capsule.

On gross examination these tumours are greasy, yellow-grey, bulky, circumscribed masses. When sectioned, the tumour appears to bulge from its cut surface. Some areas have a slimy gelatinous appearance; it is from these areas that a thick mucoid secretion may be expressed. Other areas commonly show fat necrosis, hæmorrhage, and pigmentation. Cysts are common and are frequently due to liquefaction of myxomatous areas within the tumour mass.

The histology of these tumours is extremely variable. Sections from one region may demonstrate fully differentiated adipose tissue, the frozen section of which, when stained with Sudan-red, presents the colourful picture of mature fat cells. Sections from another region may show a completely anaplastic sarcoma, the cells of which vary in shape, size, polarity, and staining characteristics. In the latter areas immature and giant lipoblasts with varying amounts of vacuolation are commonly seen.

Sections taken through the myxomatous regions reveal extensive areas of loosely woven cells, the nuclei of which are round or slightly irregular. These nuclei are rich in chromatin and stain deeply basophilic. The intracellular substance is homogeneous and faintly basophilic and stains positive for mucus.

As for liposarcomas elsewhere, these tumours can best be grouped into the following four main histological types as suggested by Stout:[8]

1. The well-differentiated myxoid type resembling embryonal fat; these tumours frequently recur locally but do not metastasize.

2. The poorly differentiated myxoid type resembling group I, but possessing large bizarre lipoblasts.

3. The round cell or adenoid type. In this group the lipoblasts are round and have a central nucleus surrounded by voluminous foamy cytoplasm. They commonly form giant cells.

4. The mixed type, consisting of a combination of the elements of the other three types.

TREATMENT

When feasible, the classical radical mastectomy is the best means of therapy, for this tumour tends to metastasize to the regional lymph nodes, and to recur in the pectoral muscles when inadequately excised. Some believe that radiotherapy may have a palliative effect and as such is indicated in treating metastatic lesions not amenable to surgical removal. Although they are slow-growing tumours, they will lead inevitably to death of the patient, as a result of metastatic spread.

DISCUSSION

The different histological picture[10] presented by many of these tumours may be somewhat less confusing if we consider the frequent tendency of many of the connective tissue tumours to undergo transition from one type to another. Although liposarcomas contain poorly differentiated pleomorphic cells, they usually show differentiation towards tissue that closely resembles normal fat. Immature fat cells are frequently abundant in rapidly growing lipomas, but this is the growth pattern of these tumours. Adult fat cells do not have the potential to proliferate. Willis[10] has cautioned against labelling a tumour a liposarcoma for no other reason than that it contains fat, for the presence of fat may be owing to degenerative changes in another type of tumour, or to a fibrosarcoma arising from the connective tissue of a lipoma.

A 76-year-old white, married woman came to the Buffalo General Hospital, Buffalo, New York, with a one-year history of a small, movable mass with the consistency of soft rubber, involving the upper outer quadrant of the left breast. This lesion originally caused no distress or disability. Recently, the mass had increased in size, reaching the mid-axillary line and displacing the breast forward. The patient was then conscious of the mass in her breast on motion of her arm, and she found that it interfered with her clothing.

Physical examination revealed a plum-sized mass in the upper outer quadrant of the left breast, associated with a few non-tender, shotty nodules in the ipsilateral axilla. The mass displaced the breast forwards and was of the consistency of soft rubber (a little firmer at its periphery). It was not attached to the overlying skin which had a mild bluish discolouration. It was not attached to the deep fascia, being freely movable in its surrounding tissue. There were no enlarged lymph nodes in the neck or left supraclavicular fossa. The right breast and axilla showed no abnormality. The remainder of the physical examination was non-contributory.

A simple mastectomy was performed with a minimum of axillary dissection. No postoperative complications were encountered. Gross examination of the excised specimen revealed a breast and overlying skin measuring 18 x 13 x 5 cm. in its maximum dimensions. On section, just beneath the skin, a large, pink, meaty tumour mass was encountered measuring 8 cm. in diameter. Adjacent to this large mass, but not connected to it, was what appeared to be a typical scirrhous duct cell carcinoma, measuring 2 x 3 x 1.5 cm. in its maximum dimensions.

Histological study revealed two separate tumours, the smaller of which was a typical scirrhous, duct cell carcinoma with infiltration of the surrounding tissue

and marked hyalinization of the stroma. The large tumour was a sarcoma of adipose tissue derivation, presenting marked changes in cell shape, size and staining characteristics. Numerous mitotic figures were seen in all fields. This tumour was a liposarcoma type IV.

Follow-up after four and a half years found the patient alive and well, clinically free of recurrent carcinoma or sarcoma.

CONCLUSIONS

Liposarcoma is a rare lesion of the breast. Unlike most sarcomas of the breast, it occasionally metastasizes to the axillary lymph nodes. Metastasis is primarily via the blood stream. When there is no evidence of metastatic spread, and factors in the individual case permit, classical radical mastectomy is the treatment of choice. Radiotherapy, when there is evidence of metastatic disease, may have a palliative effect. Liposarcoma and carcinoma may co-exist within the same breast.

SUMMARY

The literature concerning liposarcoma of the breast is briefly reviewed, and the case of a 76-year-old white woman is presented. The disease is characterized by the presence of a moderately firm, circumscribed mass, freely movable in the surrounding tissues. Often the tumour is present for more than a year before diagnosis is established. Grossly and histologically the picture is similar to liposarcoma elsewhere. It is prone to recur locally and, unlike most sarcomas of the breast, it occasionally metastasizes to the regional lymph nodes. Radical mastectomy is the treatment of choice, provided there is no evidence of distant metastases.

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FREEDOM OF VS. FREEDOM FROM

Freedom of choice means that the person is able to choose his own course of action and his own pattern of living, subject to the requirement that he shall not act so as to violate the freedom of choice of others. Freedom in this sense, it should be noted, is freedom of, not freedom from or freedom to; the preposition is of great importance, for the latter represent not different aspects of the same thing but entirely different conditions. This calls to mind the famous four freedoms enunciated by President Franklin D. Roosevelt during World War II—freedom of speech, of worship, from want, and from fear—later called "a noble pun" by the British economist, Joan Robinson. The two pairs of freedoms were, in fact, of entirely different character. Mr. Roosevelt meant security from want and fear, not freedom or liberty. Many philosophers, including Franklin and Jefferson, have pointed out that freedom and security are inconsistent human conditions. Indeed, make freedom of choice into freedom from choice and one comes close to a definition of slavery.—Editorial, *J. A. M. A.*, 172: 942, 1960.

SHORT COMMUNICATION

THE EFFECT OF NICOTINIC ACID ON HYPERCHOLESTEROLÆMIA*

RUDOLF ALTSCHUL, M.D.† and
ABRAM HOFFER, Ph.D., M.D.,‡
Saskatoon, Sask.

NICOTINIC ACID (niacin) amongst many other substances was tested as to its effect in lowering serum cholesterol levels in an effort to inhibit atherosclerosis, but with little or no effect (Jakovleva-Korchagina;[1] Albanese *et al.*[2]). Only when we increased the dose substantially, did we succeed in lowering serum cholesterol in rabbits (Altschul[3]), normal adults, and patients with various diseases (Altschul, Hoffer and Stephen[4]). In addition, development of atherosclerosis in experimental animals was inhibited (Altschul[3]). These findings were confirmed by many other authors, and today nicotinic acid in large doses (minimum 1 g. per 50 lb. body weight) is considered "one of the most uniformly active hypocholesteræmic agents yet studied" (Portman and Stare[5]). In five publications improvement or disappearance of angina pectoris attacks has been reported (Achor *et al.*,[6] Parsons *et al.*,[7] De Soldati *et al.*,[8] Goldner and Vallan,[9] Belle and Halpern[10]). The Council[11] on Drugs of the A.M.A. voted "to expand New and Nonofficial Drugs to describe the use of nicotinic acid in hypercholesteræmia".

The main side effect is cutaneous vasodilatation (flushing and itching), which usually disappears after a few days. In fewer cases, gastro-intestinal reactions occur, which are usually transient, but in some cases they necessitate discontinuing the treatment. This side effect is possibly due to the high acidity of the substance. Therefore Altschul and Hoffer[12] suggested that the pure acid be replaced by a buffered nicotinic acid—at least in patients with gastro-intestinal reaction. Other side effects so far reported (one of thyroid hypofunction,[11] one of jaundice[13]) are not proved to be causally connected with nicotinic acid therapy.

Obviously it is of great interest to establish how the large doses of nicotinic acid lower levels of serum cholesterol. Altschul[14] thought that this effect might be ascribed to increased *in vivo* oxidation, leading to the formation of oxycholesterols which are not atherogenic. Kraupp,[16] by treating animals with heparin and nicotinic acid, found that the cholesterol-lowering effect of nicotinic acid is due to a firmer binding of cholesterol to proteins, thus interfering with the analytical determination of cholesterol, but Sherber and Marcus[17] showed that heparin, added also to

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*From the Laboratory of Gerontology and Department of Psychiatry, University of Saskatchewan, Saskatoon.
†Professor and Head, Department of Anatomy and Laboratory of Gerontology, University of Saskatchewan.
‡Director of Psychiatric Research, Psychiatric Services Branch, Department of Public Health, University Hospital, Saskatoon, Sask.

normal human serum *in vitro*, will increase the yield of cholesterol. Duncan and Best[18] and Perry[19] bring forward the explanation that nicotinic acid decreases hepatic synthesis of cholesterol from acetate; according to Perry, this is due to increased oxidation. Kritchevsky[20] and his associates were able to show that nicotinic acid increases the oxidation of cholesterol by preparations of liver mitochondria.

Friedman and Byers[21] have recently advanced the explanation that the lowering of serum cholesterol by large doses of nicotinic acid in man and animals is due to anorexia. Since it appears to us that the authors have overlooked and misinterpreted the data of other authors, and since at least in two instances their conclusions are based on an error which is easily proved as such, we deem it desirable to comment on their work.

In their series A of rats given 1% nicotinic acid in their feed, the plasma cholesterol level decreased after 12 days by 25%, which the authors term only "a moderate decline". In their controls, the plasma cholesterol level decreased—for no apparent reason—by 7.5%. The first group failed to gain (293 g.: 290 g.), the three grams difference being labelled a loss of weight. This statement applies also to their second experiment, in which, however, according to their Table II the animals gained weight. This is in contrast to the findings by Unna,[24] by Handler and Dann,[25] and by Chen *et al.*[26] who found no inhibition in growth of mice, rats, chickens and dogs given large doses of nicotinic acid or its sodium salt in their food. Only two dogs of Chen *et al.*,[26] given two grams of nicotinic acid daily, died with gastro-intestinal disorders (possibly of distemper?) whereas in Unna's experiments all the dogs tolerated large doses very well.

In series B of Friedman and Byers the rats receiving nicotinic acid for 14 days gained weight (295 g.: 310 g.) although less than the controls (298 g.: 330 g.). The decrease in plasma cholesterol, according to the authors, was slight (–16%), whereas the plasma cholesterol of the controls increased, for no apparent reason, in the same time (+12.2%). If the data on weights given by Friedman and Byers in Table IV are taken at their face value for chi square analysis (for other statistical analysis, the standard errors are missing), it is found that the differences in weight are not significant.

In series D the authors gave 10 rabbits a high cholesterol-oil diet and 10 rabbits the same diet with 0.5% nicotinic acid. Of their first group "only three" (i.e. 30%) died of intercurrent infections; of the second, five (i.e. 50%). The authors consider the difference important and due to the ingestion of nicotinic acid; but a chi square test (with Yates's correction) would have proved to them that the difference in mortality is far from being significant. It appears that their rabbits had an epidemic of "sniffles" with no significant difference ($0.5 > P < 0.95$) in mortality between the group which received nicotinic acid and that which did not. It is, moreover, surprising that a 30% mortality of cholesterol-fed rabbits before the end of the three-month test is considered by the authors as "not unusual". This is certainly not in agreement with the findings of other workers and ourselves. And although the authors state: "Certainly it was our impression that the rabbits fed nicotinic acid, as a group, presented a far less healthy and vigorous appearance than the controls," the rabbits fed nicotinic acid gained as much weight (+46.39%) as the latter (+46.04%) (Table V). The plasma cholesterol level rose to 749 mg. % in the animals receiving cholesterol and nicotinic acid, but to 1020 mg. % in those without nicotinic acid. In view of the small series involved, there is no significance in this apparently considerable difference.

The authors do not accept the weight increase of rabbits fed nicotinic acid in the experiments of Merrill and Lemley-Stone,[25] "because weights of rabbits cannot be employed as an exact indicator of their food intake," thus implying that there was prolonged anorexia in association with gain of weight. In a more recent work, Cava *et al.*[29] found that rabbits receiving 0.5 g. nicotinic acid daily for three months gained 1082 g. in weight, whereas the controls gained only 986 g. The authors seem also to have overlooked Altschul's[3] short-term experiments on rabbits which showed that 24 hours after feeding of nicotinic acid in gelatin capsules the serum cholesterol level was lowered to a highly significant degree. When nicotinic acid was injected subcutaneously, a highly significant fall in serum cholesterol occurred even after four hours. Therefore, anorexia cannot have caused the decrease. Similar "acute" experiments by Kraupp[16] proved significant lowering of serum cholesterol level after administration of nicotinic acid.

As to experience with humans: Friedman and Byers,[21] who report no personal experience, state that weight changes of patients have not been published, admitting, however, that Galbraith *et al.*[28] observed no weight changes in their cases. They overlooked the findings of Achor *et al.*[6] in 16 patients, of whom six gained a combined total of 37 lb., nine lost a combined total of 37 lb. and one had no change, after one year of treatment. They overlooked, further, the report of Gurian and Adlersberg[22] that after the onset of treatment with nicotinic acid "there was an initial gain followed by a subsequent weight loss. It is of interest that the maximum decrease in serum lipids occurred during the period of weight gain." More recently, Parsons and Flinn[23] stressed the absence of significant loss of weight in patients treated with large doses of nicotinic acid. We also wish to contrast the anorexia theory of Friedman and Byers with the statement of Goldner and Vallan:[9] "Many patients indicated that their appetite had increased." Surprising is the criticism of Friedman and Byers of the report by Parsons *et al.*[7] of one case of

TABLE I.—EFFECT OF BUFFERED NICOTINIC ACID (1 G. THRICE DAILY FOR TWO WEEKS) ON WEIGHT AND SERUM CHOLESTEROL IN NORMAL VOLUNTEERS

	Weight		*Serum cholesterol in mg.%**	
Case No.	*Before*	*After 2 weeks*	*Before*	*After 2 weeks*
1	171	171	218	142
2	152	152	178	132
3	170	168	252	235
4	158	158	175	132
5	166.5	168	223	196
6	150	150	198	162
7	167	165	232	188
8	199	197	222	156
9	127	127	162	167
10	72	72	178	135
11	156	153	149	132
12	148	150	230	163
Mean	153	152.5	201.4	161.7

*From Altschul, R. and Hoffer, A.: *Brit.M.J., 2: 713,* 1958.

severe hypercholesteræmia in which the use of nicotinic acid "appeared of doubtful or slight value", which overlooks the other cases reported and also those of Goldner and Vallan,[9] amongst them one of familial hypercholesteræmia in which treatment with nicotinic acid decreased the serum cholesterol level from 1000 mg. % to 250 mg. % in six weeks "in spite of the fact that the fat intake was increased from 30 g. to 60 g. daily".

Finally, we would like to mention the following: in our investigation on the effect of buffered nicotinic acid, the weights of the volunteers were also taken, although not mentioned in the publication. We wish to add here that in the 12 volunteers in which the mean serum cholesterol value decreased by 21.44% from 205 mg. % to 161 mg. % after two weeks of daily medication with three grams of buffered nicotinic acid, the initial mean weight of 153 lb. "decreased" after two weeks to 152.5 lb. (see our Table I). In another, hitherto unpublished series of 17 schizophrenic patients, the mean weight of 151 lb. "decreased" after two weeks to 150.8 lb. after treatment with daily doses of three to six grams of nicotinic acid, whereas the mean serum cholesterol value decreased from 201.4 mg. % to 148.3 mg. % (see our Table II).

TABLE II.—EFFECT OF NICOTINIC ACID (3-6 G. DAILY) ON WEIGHT AND SERUM CHOLESTEROL LEVEL IN SCHIZOPHRENIC PATIENTS

	Weight		*Serum cholesterol in mg.%*	
Number	*Before*	*After 2 weeks*	*Before*	*After 2 weeks*
1	152	145	150	130
2	198	186	345	165
3	149	149	185	110
4	161	160	135	145
5	163	161	295	187
6	156	155	260	140
7	132	133	160	125
8	113	116	195	130
9	176	185	195	175
10	95	97	160	130
11	159	160	200	140
12	144	148	175	190
13	124	120	190	155
14	174	173	225	150
15	162	162	185	170
16	126	126	205	175
17	184	188	165	105
T	2568	2564	3425	2522
N	17	17	17	17
Mean	151.0	150.8	201.4	148.3

SUMMARY

The work of Friedman and Byers,[21] leading them to the conclusion that the cholesterol-lowering effect of large doses of nicotinic acid is due to anorexia caused by this medication, is reviewed. It is pointed out that the findings of these authors are not in agreement with the findings of other authors, and that, further, not all of their own findings support their dictum; that some of the pertinent literature has been overlooked and some data have been misinterpreted. More recent reports by other authors and new findings by ourselves also contradict the view of Friedman and Byers.

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TALKING AND LISTENING

The editor of the *Bulletin of the College of General Practice* has employed his usual talent for provocative discussion in his comment on the place of talk in general practice (January 1960). Just how it is estimated that talk forms 60% of work in practice is not quite clear: at times silence may be golden. But the statement is a useful opening gambit.

There is not much doubt that the physician must establish rapport with his patient and that this calls for communication. In a setting, as in medicine, where there is need on the one hand and a desire to help on the other, there should be little trouble in this reciprocal arrangement.

Is it not the case, however, that often it is the very outpouring of his mind that the patient desires, and the receptivity of the physician which is all important? Here it is that he is most liable to fail his patient who "may be difficult, socially insignificant, or medically uninteresting", and will consequently test that rare virtue, patience.

Again, it is not so easy, even with patient effort, always to "explain things". It takes but little experience in medicine to realize that. It may be that we do not try to simplify our terms enough: few patients will ask to have words explained to them. In spite of the incessant "popularization" of medicine, it still does no harm to speak of a broken bone rather than a "fracture", or a stroke rather than a "cerebral accident". Coronary thrombosis in high places has received such microscopical scrutiny and documentation in the press that one might almost feel that it had become a part of the daily vocabulary, but a casual examination as to its definition might reveal some queer pathological conceptions. How often too does a doctor's apparently quite clear account lead to questions which cannot be answered with such complete assurance, with corresponding misconceptions in the patient's mind?

These are some of the difficulties inherent in the use of technical language. It is worth noting that even workers themselves in technical fields may have trouble in the interchange of ideas with other specialties. Does not the phraseology of psychiatry, for example, slow up the understanding of its point of view?

In the fields of science and the humanities intercommunication is becoming more and more impossible. The physicist, say, and the scholar find no common mental ground, no cultural pulmonary system for exchange and ventilation of ideas. This is well brought out by Sir Charles Snow,* who feels that if the scientist may be accused of not reading as widely as he should, the scholar on his side is not well enough versed in the basic assumptions of science. He also implies that it is the scientific approach on which our future depends. Even if this conclusion is open to doubt, there is no question of the drifting apart of the two disciplines; the closing of the gap should be an educational objective.

So then there must be a continual struggle to keep our lines of communication open, between the advance of discovery and those who can only follow more slowly.

An effort similar in kind is needed in general practice, but here it is more to overcome the handicaps of pressure and to maintain the high standards of thoughtfulness required in the care of the sick.

Editorial Comments

℞ FOR SUCCESSFUL TRANSFUSIONS

The maximal survival of transfused red cells forms an essential criterion of successful blood replacement therapy. But what of those cases in which elimination of the donor cells is hastened; if serological incompatibility is the cause, how can this best be detected in advance?

During the last five years or so, Mollison and his co-workers at the Medical Research Council Blood Transfusion Research Unit, Hammersmith, have done much to correlate the *in vitro* characteristics of blood group antibodies with their behaviour against incompatible red cells *in vivo*. This work has recently been reviewed by Mollison in the Oliver-Sharpey Lectures at the Royal College of Physicians of London.[1, 2]

Most blood group antibodies are capable of bringing about red cell destruction *in vivo*; but some antibodies are more effective than others. By the experimental use of incompatible red cells tagged with Cr^{51} or P^{32} and injected into recipients with various blood group antibodies, it has been possible to estimate the proportion of the transfused cells that are destroyed and their rate of destruction. These experimental findings can be correlated with the results following larger transfusions of in-

*Snow, C. P.: The two cultures and the scientific revolution, The Macmillan Company of Canada Limited, Toronto, 1959.

compatible blood so far as the proportion of cells destroyed is concerned; but the pattern of elimination after a large transfusion may differ considerably from that following the injection of 1 ml. of incompatible blood.

On the basis of their *in vitro* reactions, blood group antibodies may be divided into those that react well at 37° C. and those that do not. Either class of antibody may sensitize cells to an anti-human globulin (Coombs) serum. Of those that react in this way, some require the presence of complement—a non-gamma globulin—and an anti-human globulin serum that contains potent anti-non-gamma globulin components; for, when the antibody is complement-binding "the anti-globulin serum reacts with complement adsorbed on to the sensitizing cells rather than with the antibody itself".[1-3] Most antibodies in the ABO, P, Lewis and Kidd systems show some degree of complement-dependence, and so do a number of examples of anti-Kell and anti-Duffy.

Any degree of agglutination of the donor cells by the recipient's serum at 37° C. *in vitro* invariably leads to at least their partial destruction when transfused. If agglutination in saline at 37° C. is absent but the indirect anti-globulin test is positive, the survival of the donor cells will largely depend upon the antibody characteristics: incomplete antibodies that do not bind complement, such as anti-Rh, cause low red cell destruction even when the titre is as low as 1:4, whereas even weak complement-binding antibodies generally cause quite rapid elimination of incompatible cells.

Inability of the recipient's serum to agglutinate donor cells at 37° C. *in vitro* does not, however, necessarily mean that the cells will survive normally when transfused. If agglutination is strong at 20° C. and is still present at a temperature approaching 37° C., partial destruction of the donor cell population may be expected; while antibodies that agglutinate cells at a maximum temperature of 25° C., such as anti-P, may fix complement at 37° C. and cause quite rapid cell destruction.

Although it is the most recent addition to the battery of tests that nowadays form the compatibility test, the indirect anti-globulin method is the most important member. Without this test, many "warm" incomplete antibodies such as anti-K, anti-Fy^a, and some examples of anti-Rh, will be missed; complement-dependent antibodies such as anti-Jk^a may not be detected; and the importance of some "cold" antibodies capable of binding complement—of which anti-Le^a is the best example—will not be realized.

The performance of the indirect anti-globulin test has been complicated by the need to pay attention to antibodies showing varying degrees of complement-dependence. Firstly, as complement is thermolabile, the serum to be tested should either be fresh, or stored at 4° C. for not more than about 24 hours. Secondly, anti-globulin sera vary in the spectrum of their reactivity from batch to batch and—more important—from manufacturer to manufacturer;[4] in the absence of any published governmental standards either in this country or in the United States covering the question of complement-dependent antibodies, each blood bank should make certain that the anti-globulin serum selected is capable of detecting them.

As each bottle transfused contains more than one incompatible blood group antigen that may initiate an antibody response, a satisfactory compatibility test cannot be taken as a guarantee that donor red cell survival will be maximal. But a compatibility test that includes the indirect anti-globulin method even for emergency use will, in the proper hands and with a good Coombs serum, minimize the risk of increased blood destruction.

B. P. L. MOORE

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INJECTION OF VARICOSE VEINS

The use of sclerosing solutions in the treatment of varicose veins has become unpopular; indeed some teachers of surgery warn their students against sclerosing therapy even as an adjunct to the operative treatment of varicose veins. However, many who have had wide experience with varicose veins know that this is merely a swing of the therapeutic pendulum far past the median and that the real worth of sclerosing therapy needs re-emphasis. Erkki Saarenmaa, a university lecturer of surgery from Helsinki, Finland, in *Acta Chirurgica Scandinavica* (Supp. 241: 1, 1959), writes strongly in favour of sclerosing therapy. His monograph, "The Varicose Syndrome of the Lower Limb", provides a multitude of excellent photographs illustrating his methods and his results and is well worth reading, though Saarenmaa's use of sclerosing solution appears much too radical. Yet apparently he has encountered few of the complications that huge dosages, through multiple injection sites at one treatment, might bring about. Even his method of keeping post-injection and postoperative patients flat in bed for 24 hours seems to have netted him only one pulmonary embolic death in some 3000 patients treated between 1939 and 1957 (from the text, however, one suspects that there have been other embolic sequelæ—a result not unexpected).

The present unpopularity of sclerosing therapy, once so widely acclaimed, seems to stem from previous misapplication of the method, misuse of the various sclerosing agents, and various misconceptions about the nature of varicose veins and their treatment.

First, among older doctors, there is the memory of many patients returning, sooner or later, for more injections to close recurrent varicosities. Often enough, both patient and doctor were irked by this seemingly endless routine. However, this was not the fault of the sclerosing therapy in itself, but of misapplication of treatment. If injection therapy alone is confined to small isolated varicosities, not connected with incompetent long or short saphenous veins or with incompetent perforators, and if proper techniques are used, prolonged

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closure will ensue without complications. For large varices, connected with or comprising incompetent long or short saphenous veins or incompetent perforating veins, injection should be used only after surgical stripping, ligation and excision of such veins has been done. In cases where this routine is followed, long-term results are excellent.

Second, when sclerosing therapy was popular, not only was it too frequently misapplied, but the fundamental rules of its use were often disregarded. The commonest faults were use of too much solution, use of too strong a solution, injection of too many sites at one treatment, injection of both legs at one visit, and injection of solution outside the vein lumen; or injection in the presence of inflamed or precariously nourished skin, arterial insufficiency, cardiac or renal failure, acute or subacute superficial or deep phlebitis, various blood dyscrasias and pelvic tumours or other causes of lower-limb venous back pressure. Many of the critics of sclerosing therapy have not seen the method properly carried out. In fact, many people using sclerosing solution today give doses that can be dangerous or employ techniques that may cause complications.

Third, there was always the fear that deep vein damage might result from some of the sclerosing solution spilling into these veins; and the tendency of many in recent years to overemphasize the role of deep vein pathology in varicose veins has enhanced this fear. But many have demonstrated radiologically that with proper care this danger was negligible; while in a large and active vein clinic which the writer was associated with for many years, where the technique was meticulous and conservative, no deep vein complication was ever seen that could be attributed to sclerosing therapy.

Moreover, in recent years a return to more radical operative treatment for varicosities has been held by many to make concomitant or follow-up sclerosing injections unnecessary. Accurate follow-up of patients who have had adequate radical operative treatment shows that new varicosities will sooner or later appear in many patients, and if these varices are not injected when small they will enlarge until another operation is necessary. Most patients prefer an occasional injection to further operation.

There is also a tendency to forget that, although many patients with varicose veins will never develop dermatitis, ulceration, phlebitis or thrombosis, or experience a serious hæmorrhage, it is never certain which patient will develop these complications. Therapy is directed primarily to preventing these sequelæ which are more easily prevented by early sensible conservative therapy than alleviated with much trouble by strenuous methods later on.

Returning to Saarenmaa's monograph, we may say that several of his statements and methods provoke comment. Saarenmaa carries out sclerosing therapy, as a rule, by inserting numerous needles into the varicosities while the patient stands, allowing blood to pool on the floor; then the patient is placed horizontally and up to 27 c.c. of sodium morrhuate, divided among the various sites, is injected. This technique is unæsthetic to say the least. Although he claims at first that the clot thus formed is fibrinous, sticks to the vein wall and does not spread, he later admits that such clots do spread, sometimes to close all superficial veins to the groin, and that they do become friable, soft and non-adherent distal to the injection sites. One excellent photograph points up very sharply the dangers of the method. It shows a high long saphenous ligation being done, as is Saarenmaa's routine, the day after injection; in this case only one distal site was treated and only 10 c.c. sodium morrhuate was used. A soft friable clot is lying loose at the sapheno-femoral junction. One wonders, with marked trepidation, what happens when more solution at numerous sites is used. Actually the author makes out that the more solution used, up to his maximum, the more adherent and less dangerous the clot. He also tries to show that it is better to tie the vein after injection than before. Few will agree with this. Saarenmaa's sclerosing agent is sodium morrhuate, which he admits causes allergic reactions, nausea, vomiting and fever in some cases. Many clinics have discarded this solution as too dangerous, even in small doses, and use ethanolamine oleate or sodium sotradecol in doses of 0.5 to 3 or at most 5 c.c. at one treatment with the precautions noted above; necessary operative procedures are performed first. Saarenmaa not only performs high ligation after more or less drastic injections but he keeps post-injection and postoperative patients in bed for 24 hours. In reviewing the literature on varicose veins, one finds that embolism is much more common in patients confined strictly to bed after therapy. Saarenmaa deprecates the more radical operative procedures, for instance Linton's operation, although he does popliteal vein ligations, excision of ulcers and skin grafts in appropriate cases. There is good evidence that "high" ligation or triple or quadruple ligation, even when combined with sclerosing therapy, allows earlier recurrences than thorough stripping, ligation and excision of incompetent varices with a meticulous search for and eradication of incompetent perforators. There is ample evidence that "peep-hole" incisions result in early recurrences, because of missed perforators, subfascial or even epifascial incompetent venous channels.

In summary, sclerosing treatment of varicose veins, with proper safeguards, is still an excellent method. Although dogmatic statements and stereotyped methods are out of place in a discussion of varicose vein treatment, a working rule might go as follows. Small varices, not connected with incompetent long, short or perforating veins, can be closed safely and efficiently by ambulatory injection therapy; sometimes excision of groups of such veins under local anæsthesia is useful. Large varicosities, connected with incompetent long, short or perforating veins, should be dealt with by adequate operation, the patient kept as ambulant as possible, and residual veins sclerosed by postoperative injections. Between these two groups will be some cases better dealt with, for various reasons, by simple ligation and excision, combined with, or followed by, sclerosing treatment.

Medical News in Brief

SEDIMENTATION RATE OF WHITE BLOOD CELLS

As a result of original research by Storti and his co-workers at the Institute of Pathology of the University of Modena (Italy), a method was developed for determining the sedimentation rate of white blood cells. Bellesia and Grignaffini, of the same Institute, report their studies of the factors responsible for the alterations in sedimentation rate of white blood cells (*Schweiz. med. Wchnschr.*, 90: 64, 1960). As in the case of the sedimentation rate of red blood cells, three factors were considered: (1) the plasma, (2) the corpuscles and (3) the number of cells per unit. The technique of Storti permits the use of a more or less constant number of white cells in any given test so that the third factor is eliminated. By performing the sedimentation rate test in two stages, the authors were able to study the influence of qualitative and quantitative changes of the albumin and globulin of the plasma and the quantitative changes of fibrinogen on the sedimentation rate. Finally, by crossing white blood cells of normal subjects with plasma of abnormal blood and the white blood cells of abnormal blood with plasma of normal subjects, they were able to prove that in the plasma the only variable of importance was that of fibrinogen. When the fibrinogen content of the plasma is markedly elevated, it exerts a marked influence on the sedimentation rate of the white blood cells suspended in this particular plasma. On the other hand, suspension of abnormal white cells in normal plasma produces an elevated rate. Thus the globular factor—that is, the shape and size of the white blood corpuscle—is the most important one in an increased sedimentation rate of white blood cells.

INTRAVENOUS FIBRINOLYSIN (PLASMIN) IN MAN

Seventy-two infusions of human fibrinolysin were carried out by Moser (*Circulation*, 20: 42, 1959) in 63 hospital inpatients to assess the coagulation changes, fibrinolytic activity, and systemic consequences that follow such infusions at various dosage levels.

The effects upon coagulation factors were minor at all dosage levels. Fibrinogen content was depressed more frequently and to a greater extent than any of the other factors measured. No hæmorrhagic phenomena were noted in any of the patients, including 29 who were receiving anticoagulant drugs simultaneously.

Systemic toxicity was limited primarily to a febrile reaction present in 44% of the total patient-group. The source of pyrogenicity remains undefined, but appears related either to nonactivator residuals contained in fibrinolysin or to products released by the action of fibrinolysin upon thrombotic material.

Fibrinolysin infusion consistently enhanced plasma fibrinolytic activity at all dosage levels. The intensity and duration of such enhancement appeared related to fibrinolysin dosage.

However, a number of clinical and laboratory questions regarding fibrinolysin must first be answered before firm statements can be made regarding the proper application and therapeutic value of this material in human thromboembolic disease.

SIGNIFICANCE OF PLEURAL EFFUSION COMPLICATING OTHERWISE OPERABLE BRONCHOGENIC CARCINOMA

Bronchogenic carcinoma complicated by pleural effusion presents a difficult problem in management, especially when the patient appears otherwise suitable for operation. Most surgeons are agreed that the presence of malignant cells in pleural effusion indicates inoperability, but the significance of fluid in which malignant cells are not seen is debatable.

In order to establish the significance of pleural effusion in otherwise operable patients, 360 cases of bronchogenic carcinoma from a large U.S. hospital between 1936 and 1955 were reviewed by Brinkman (*Dis. Chest*, 36: 152, 1959). There were 21 with pleural effusion who had no evidence of secondary spread elsewhere and, as far as could be judged clinically, were operable and potentially curable patients.

All 21 patients underwent thoracotomy, at which time 17 were found to have mediastinal involvement, and five had obvious pleural secondaries as well. Eleven of these 21 were considered inoperable; the other 10 had pneumonectomies, eight of which were on the left side. In six this was a palliative procedure, with subsequent survival varying from one to 24 months. The mean survival time was seven months, compared to a mean survival for untreated bronchogenic carcinoma of 4 to 6½ months. Four patients had pneumonectomy with removal of all recognizable tumour. However, three of these died within six months of operation.

Pleural effusion, with or without demonstrable malignant cells, is of serious prognostic significance. It is questionable whether a major procedure such as pneumonectomy, especially in an elderly person, is justified when the chance of cure is so poor.

BLOOD PRESERVATION

The preservation and storage of blood for emergency use as in the treatment of mass casualties is always a problem both in the armed forces and in civilian medicine. At the U.S. Naval Hospital, Chelsea, Massachusetts, a special laboratory has since 1957 been exploring possible methods, and in collaboration with the Protein Foundation, Inc., Boston, has been studying the use of red blood cells preserved in glyceryl at low temperatures (L. D. Heaton: *Armed Forces M. J.*, 11: 4, 1960). Fresh blood is centrifuged to separate the red cells, which are placed in glyceryl and immediately frozen. At any time up to 28 months later, rapid thawing and reconstitution in 5% albumin solution results in what appears to be a reasonably acceptable substitute for fresh whole blood. The oxygen carrying capacity is about the same as that of fresh blood, and at present the medical and surgical services of the hospital in Chelsea are using reconstituted blood preserved in the manner described. Frozen blood, in addition to its potentialities for limited stock-piling, has the advantage of eliminating commonly encountered losses caused by outdating, and will allow the storage of the patient's own blood for elective surgery whenever there is a special problem or rare blood type or unusual immunological reaction.

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MEDICAL SOCIETIES

CHANGES IN THE TRAINING REQUIREMENTS FOR THE EXAMINATIONS OF THE ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF CANADA

At its meeting in January 1960, the Council of The Royal College of Physicians and Surgeons of Canada revised the regulations relating to the training requirements for the examinations of the College in a number of specialties. The objective of the amendments has been to provide a single standard of training for both the Fellowship and Certification examinations in the specialties concerned. No change was made in the regulations relating to the Certification examinations in these specialties.

The new requirements are reproduced below in full. In each case they represent the training requirements for both the Fellowship and Certification examinations in the specialty. The year shown in parentheses after the specialty indicates the year in which the new regulations become applicable. In that year, candidates for either the Fellowship or Certification examinations in these specialties must have completed training in accordance with the new requirements. Candidates planning to take the examinations prior to the year shown will continue to have their training assessed in accordance with the published regulations dated May 1956 and reprinted September 1959.

TRAINING REQUIREMENTS FOR THE EXAMINATIONS IN ANÆSTHESIA (1965) FELLOWSHIP OR CERTIFICATION

1. An approved general internship of at least one year.
2. Four years of graduate training in addition to the general internship. This period must include:
   - (a) One year of approved resident training in Internal Medicine, or six months of approved resident training in Internal Medicine and six months of approved resident training in General Surgery.
   - (b) Two years of approved resident training in Anæsthesia.
   - (c) One year of training which may include:
     - (i) One further year of approved resident training in Anæsthesia.
     - (ii) One year as a clinical research fellow in a department approved by the College.
     - (iii) One year in the full-time study of basic science in a department approved by the College.
     - (iv) If no time was spent on surgery under 2(a), six months of approved resident training in surgery and six months of approved full-time study of basic science.
     - (v) One year in an approved course of study and training at a hospital or university centre in Canada or abroad.

TRAINING REQUIREMENTS FOR THE EXAMINATIONS IN INTERNAL MEDICINE (1964) FELLOWSHIP OR CERTIFICATION

1. An approved general internship of at least one year.
2. Four years of graduate training in addition to the general internship. This period must include:
   - (a) Two years of approved resident training in Internal Medicine.
   - (b) Two years of training which may include:
     - (i) Further approved resident training in Internal Medicine,
     - (ii) One or more years of approved training in one or more of the special branches of medicine, such as psychiatry, neurology, tuberculosis, cardiology, etc. This period may include resident training and clinical fellowship.
     - (iii) One or more years as a clinical research fellow in a department approved by the College.
     - (iv) One year in the full-time study of basic science in a department approved by the College.
     - (v) Six months of approved resident training in general surgery and six months of approved full-time study of basic science.
     - (vi) One year in an approved course of study and training at a hospital or university centre in Canada or abroad.

TRAINING REQUIREMENTS FOR THE EXAMINATIONS IN PATHOLOGY (1960) FELLOWSHIP OR CERTIFICATION

1. An approved general internship of at least one year.
2. Four years of graduate training in addition to the general internship. This period must include:
   - (a) Two years of training in pathological anatomy in an approved hospital or other approved institution. One of these two years must be devoted to autopsy work.
   - (b) One year of approved training in clinical pathology, including hæmatology, chemical pathology, bacteriology and blood bank management.
   - (c) One year of training to include one of the following options:
     - (i) One year in the study of pathological anatomy as under 2(a).
     - (ii) One year in the further study of clinical pathology in an approved laboratory.
     - (iii) Six months of approved resident training in internal medicine and six months of approved training in clinical pathology; or six months of approved resident training in internal medicine and six months of approved resident training in general surgery; or one full year of approved resident training in internal medicine.
     - (iv) One year in the full-time study of basic science in a department approved by the College.
     - (v) One year in an approved course of study and training or research at a hospital or university centre in Canada or abroad.

TRAINING REQUIREMENTS FOR THE EXAMINATIONS IN PHYSICAL MEDICINE AND REHABILITATION (1964) FELLOWSHIP OR CERTIFICATION

1. An approved general internship of at least one year.
2. Four years of graduate training in addition to the general internship. This period must include:
   - (a) One year of approved resident training in Internal Medicine or six months of approved resident training in Internal Medicine and six months of approved resident training in General Surgery.
   - (b) Two years of approved resident training in Physical Medicine and Rehabilitation.
   - (c) One year of training which may include:
     - (i) One further year of approved resident training in Physical Medicine and Rehabilitation.
     - (ii) One year in the full-time study of basic science in a department approved by the College.
     - (iii) Six months of approved resident training is recommended in Orthopædic Surgery and six months in Neurology.
     - (iv) One year in an approved course of study and training at a hospital or university centre in Canada or abroad.

TRAINING REQUIREMENTS FOR THE EXAMINATIONS IN GENERAL SURGERY (1964) FELLOWSHIP OR CERTIFICATION

1. An approved general internship of at least one year.
2. Four years of graduate training in addition to the general internship. This period must include:
   (a) Two years of approved resident training in Surgery. One of these years must be on a general surgical service; the remaining year may also be spent on a general surgical service or, as an alternative, may be divided between special surgical services if such services are approved.
   (b) Two years of training which may include:
      (i) Further approved resident training in General Surgery.
      (ii) One year as a clinical research fellow in a department approved by the College.
      (iii) One year in the full-time study of basic science in a department approved by the College.
      (iv) Six months of approved resident training in Internal Medicine or six months of approved full-time study of basic science.
      (v) One year in an approved course of study and training at a hospital or university centre in Canada or abroad.
      (vi) One year of approved resident training in Internal Medicine.

TRAINING REQUIREMENTS FOR THE EXAMINATIONS IN OBSTETRICS AND GYNÆCOLOGY (1964) FELLOWSHIP OR CERTIFICATION

1. An approved general internship of at least one year.
2. Four years of graduate training in addition to the general internship. This period must include:
   (a) One year of approved resident training in General Surgery, or six months of approved resident training in General Surgery and six months of approved resident training in Internal Medicine or Pathology.
   (b) Two years of approved resident training in Obstetrics and Gynæcology. This must be of such a nature as will provide adequate training and experience in each branch of the specialty.
   (c) One year of training which may include:
      (i) One further year as under 2(b).
      (ii) One year as a clinical research fellow in a department approved by the College.
      (iii) One year of full-time study of basic science in a department approved by the College.
      (iv) If no time was spent on Internal Medicine under 2(a), six months of approved resident training in Internal Medicine and six months of approved full-time study of basic science.
      (v) One year in an approved course of study and training at a hospital or university centre in Canada or abroad.

TRAINING REQUIREMENTS FOR THE EXAMINATIONS IN OTOLARYNGOLOGY (1964) FELLOWSHIP OR CERTIFICATION

1. An approved general internship of at least one year.
2. Four years of graduate training in addition to the general internship. This period must include:
   (a) Three years of approved training in Otolaryngology, two years of which must be spent in approved resident training in Otolaryngology and one year of which may be spent in further approved resident training in Otolaryngology or such other training in Otolaryngology as may be approved by the Credentials Committee.
   (b) One year of training which may include:
      (i) One year of approved resident training in General Surgery.
      (ii) Six months of approved resident training in General Surgery and six months of approved resident training in Internal Medicine.
      (Either (i) or (ii) are preferred but not mandatory.)
      (iii) One year in the full-time study of basic science in a department approved by the College.
      (iv) One year in an approved course of study and training at a hospital or university centre in Canada or abroad.
      (v) One year as a clinical research fellow in a department approved by the College.

Association Notes

LADIES' PROGRAM AT BANFF

Monday, June 13

Registration: Library, Banff Springs Hotel.
Morning coffee.

Tuesday, June 14

Registration. Morning coffee.
Trip to the top of Sulphur Mountain in gondola lift.
Afternoon tour of Banff School of Fine Arts, and tea.
Western barbecue on Hotel grounds. Dress, western or informal.

Wednesday, June 15

Registration. Morning coffee.
Cocktails and luncheon, Banff Springs Hotel. Western skit and entertainment by Edmonton doctors' wives.
Evening: The Annual General Meeting, President's reception and dance (Hotel ballroom).

Thursday, June 16

Registration. Morning coffee.
Golf, bridge, presentation of golf prizes. Afternoon tea in the golf club house.

Friday, June 17

Farewell buncheon at 11.30 o'clock in the Hotel.

LETTERS TO THE EDITOR

QUESTIONNAIRE ON HEALTH INSURANCE

The circulation of the Questionnaire on Health Insurance to 20,000 Canadian physicians has resulted in a prompt and overwhelming response to the inquiry. Although no conclusions are possible until the replies are tabulated and assessed, it is permissible to say that the profession appears to be receptive to this study of their views. Many members of the Association have indicated their approval of the current survey of professional opinion but it is not to be expected that all doctors will receive the document so favourably. As

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an example of the latter viewpoint, we publish hereunder the letter of an anonymous correspondent.

To the Editor:

It will probably do no good to send this note as an appendix to the Questionnaire. In my discussions with several other members of our profession it seems that they could not care less about what is foredoomed in Saskatchewan. Therein lies our weakness. Bevan saw it and Douglas sees it. I sincerely believe that government medicine will be poor, lazy, uninspired, "safe" practice. Why does not our profession take a *public firm fighting* stand on this matter? If we are going to end up in Hell we might as well arrive disliked and fighting for what we believe to be true, as afterwards it will not matter anyway.

I have had experience *in Canada* with the spirit of government medicine and would like to suggest our weaknesses and needs as follows:

1. Our Association executives, who are after all very responsible in this, have failed to mobilize our profession against what they are in for. This should have been done long ago. They actually seem willing to play along with health department people who all want state medicine and who sit drooling for the day when they take over—new jobs galore, new prestige and power for the incompetent, more administration to make them look busy and knowledgeable, revenge against their able confreres whom they envy and resent in contrast.

2. Right in our Association across Canada medical men—some even well known to favour strongly government medicine—hold prestige positions on executives. Why is this? Why haven't they been treated as they deserved long ago?

3. Medical men, holding by connivance, ability or what have you, positions of prestige in our profession—especially university medical school teachers, and directors of key private medical agencies such as cancer, heart, Red Cross, etc.—have signally avoided making their voices heard publicly against government medicine. Why? Do they agree with it? Are they playing it safe for their jobs? Do they see a chance to organize their empires a little further? Why have they held back in Saskatchewan? Are they a special privileged group, an aristocracy who are above the dirt and risk of the battle? These are the people who are always trumpetting socialistic measures under the phony guise of "improving the standard of medicine" when 99% of the time they are only trying to improve their own chances. These are the "closed hospital" people, the appointment-by-degree people when it suits their control, the organization addicts with themselves at the top. These are the people too important to make house calls, night calls, to work weekends. These are the people always phalanxed by interns and residents whose main job is to shield them from ever being caught on call. In fact, these are the people who are selling us out to government which controls them already through research grants, salaries and other unearned handouts. Douglas specifically referred to them in his speech as "happy in the harness", so why not the rest of us? Let me hear one single dean or professor in our medical schools get up in public and denounce the politicians for what they really are and I will regain a little hope for the future of medical practice. Otherwise I think this questionnaire approach is nonsense and an example of parkinsonian-created work and waste. These prestige people will keep quiet and whatever way things fall they'll be on the right side, their jobs secure!

4. I strongly suspect that the majority of our English emigrants are in favour of the same system in Canada which they claim they have fled from in England. At any rate it is no coincidence that they have to a large degree sought out secure jobs in government or university when they got here.

We are not being harnessed to the state because we have done a poor job in Canada or because the public dislikes us. We are political pawns. We are walking to the slaughter-house like a bunch of serene and stupid sheep, with our leaders ducking to the side into their safe pens at the last moment as in England, safe in their university-privileged positions, their self-created closed hospitals, their government-subsidized private practices, their God-like self-assurance on ethics. You take a good long sniff at the politics within medicine and you'll catch the smell—the smell of rotten privilege.

So well organized has medicine become in much of Canada that I could not safely sign this letter. But I challenge the Association to publish it unsigned. It has too much hard truth to make this likely or to go down well. But I can say this, the day state medicine comes to B.C. (as it is coming next year to Saskatchewan—medicine run by a government health department will be state medicine, let's not fool ourselves) I will stop paying dues to the Canadian Medical Association as from then on it will be merely an empty plaything as the B.M.A. is in England, "full of sound and fury", accomplishing exactly nothing.

A B.C. DOCTOR

February 29, 1960.

CYCLOPHOSPHAMIDE (ENDOXAN; PROCYTOX)

To the Editor:

Frank W. Horner Limited are currently making available in Canada a new nitrogen mustard derivative from Europe, cyclophosphamide (Endoxan), which is being marketed here under the trade name of Procytox. Horner's most recent communication to the medical profession on this subject, dated January 8, 1960, is headed "Supplies of Procytox, the new cancer chemotherapeutic agent, are now available in hospitals and pharmacies", and goes on to state that "the compound . . . can be readily procured by retail pharmacies through drug wholesalers or directly from Horner."

Prominent in much of Horner's literature regarding this drug is the statement that "Procytox has been found of value in preventing relapses in carcinomas and sarcomas." This statement would seem to invite very widespread use of this new drug in the treatment of all kinds of malignant disease, even when the patient is well and his disease temporarily arrested.

A month ago I wrote to Frank W. Horner Limited asking for the evidence on which this particular claim was based, since I could not find anything to justify it in the detailed literature which they had made avail-

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NEWS & VIEWS
ON THE ECONOMICS OF MEDICINE

Prepared by the Department of Medical Economics. The Canadian Medical Association

NUMBER 5

Our sources of information are private communications and published comments in medical journals and the lay press. These are usually reliable but incorrect quotation or interpretation is always possible.

On March 29th the College of Physicians and Surgeons of Saskatchewan presented the following letter to Premier Douglas:

"The Council of the College of Physicians and Surgeons of Saskatchewan met in Regina, Saturday, March 26th. Its main purpose of assembling was to carefully weigh the public interest which the profession would serve by appointing three doctors to the government's proposed Medical Advisory Committee.

There was a thorough review of all the correspondence between your government and the College dating back to your first official notice of an Advisory Committee on December 30th, 1959. There was also detailed discussion of the points verbally raised and agreed upon by both the profession and government at meetings in your office.

From our deliberations, Council has concluded that your government has agreed that the existing terms of reference of the Medical Advisory Committee are sufficiently broad to allow a full, unobstructed study by Committee members of all the health needs of the people of Saskatchewan as they relate to medical care of patients. We feel that both your government and the profession realize that one of the duties of the Medical Advisory Committee will be to study existing medical programmes and to make recommendations for improvement where it is deemed necessary.

However, we must say that we have been disturbed to both hear and read about statements made by yourself and other members of your government which only refer to the preconceived plan of your party to institute a compulsory, province-wide and government-controlled medical care plan.

We must again refer to the resolution unanimously passed by the annual meeting of the College in October, 1959, which stated:

'We, the members of the College of Physicians and Surgeons of Saskatchewan oppose the introduction of a compulsory government-controlled province-wide medical care plan and declare our support of and the extension of health and accident benefits through indemnity and insurance plans.'

We must govern our future actions by our Statement of Policy which outlines the basic freedoms, democratic rights and the responsibilities of the people of Saskatchewan and the doctors of this province as the recipients and providers of medical services.

(over)

These points being very clear to both your government and the medical profession, the College of Physicians and Surgeons of Saskatchewan is pleased to announce the appointment of three doctors to the Medical Advisory Committee.

It is recognized by the College that these men serve on the Medical Advisory Committee as individual members and remain at liberty to express their personal opinions. It is also recognized that any segment of the Medical Advisory Committee may, if it so wishes, bring in a minority report at the conclusion of the Committee's deliberations." (1)

Mr. Douglas stated that his government has agreed to broaden the terms of reference of the Advisory Committee on Prepaid Medical Care. He said that he would not impose a time limit on the Committee's deliberations. "I presume we'll get interim reports, but we must allow the Committee all the time it needs."

The Committee will decide when to start investigations but Mr. Douglas stated: "I don't see how they can hold public hearings before midsummer or next fall." He also stated that it was unlikely that a medical care bill would be introduced at this session. "The government had hoped to submit the bill to the Committee before introducing it. It would be unfair to introduce the bill without giving the Committee a chance to study it."

Asked whether the government's five principles (News and Views January 16, 1960) still held good, Mr. Douglas said:

"The government has expressed its opinion through these principles about the form a medical plan should take, but the Committee is free to make any recommendations it likes, and the government is bound to give them very careful and thorough consideration, whether they come within those principles or not." (2)

REFERENCES:

(1) Private Correspondence, March 29, 1960.
(2) Regina Leader-Post, March 30, 1960.

(Continued from page 792)

able to the profession. In a most courteously worded reply, dated December 17, no evidence whatever was offered, it being stated that "this claim was made inadvertently". It was intimated that this phrase would not be repeated in future communications.

The latest Horner brochure, enclosed with their letter dated January 8, repeats the same claim, using exactly the same wording and printing it in a prominent position in the opening sentence of the paragraph marked "Indications".

The statement is also now made that "Procytox is quite inert in the body until it reaches malignant tissue." This would appear to be a gross exaggeration of certain theoretical advantages claimed for this drug and described in more guarded language in other parts of Horner's brochures. If this statement was true, one would have to suppose that a person not suffering from malignant disease could take this drug without any risk of depression of the white cell count or other toxic effects.

Over-exuberant advertising of this kind seems to be creeping more and more into some of the announcements which we all receive in the mail from our colleagues in the pharmaceutical industry. In this instance, where a much publicized "cancer chemotherapeutic agent" is being made so freely available, it would seem to be important that the promotional literature on the subject should be so far as possible free from statements which are in any way exaggerated or which cannot be supported by medical evidence. Nor is it sufficient, in my view, for a manufacturing firm to say in their defence that a misleading statement in one part of their leaflets is corrected by more accurate details in another part.

T. B. BREWIN, M.B., M.R.C.P., D.M.R.T.

Hamilton Clinic,
The Ontario Cancer Foundation,
Hamilton General Hospital,
Hamilton, Ont.,
January 15, 1960.

RESUSCITATION METHODS

To the Editor:

It is obvious that Dr. Donald Grant has given considerable thought to the contents of his letter on the problem of artificial respiration (*Canad. M. A. J.*, 82: 442, 1960), but I feel that he has taken a rather narrow view of this subject.

He is probably quite right that the Schafer and Holger Neilsen methods have been effective when performed by members of the Power Commission of Ontario on their fellow workers—particularly since these methods are practised every month. Dr. MacLachlan's recent article attests to this. He is quite right also when he points out the situations where one cannot discount the value of performing direct artificial respiration (mouth to mouth, mouth to nose). However, he does not stress the point that direct artificial respiration is the *only* method which can be applied in many of the situations where suffocation is about to claim the victim, and aside from the vigorous, healthy teams of men described from his experience, the methods he lauds are quite ineffective in the elderly, the obese and those involved in the multitude of daily accidents (automobiles, trains, factories, etc.) where it is usually not possible to lay out the victim in a position where the back can be squeezed or the arms can be pulled, in the short time which might mean the difference between life and death.

The technical difficulties which are listed for performing direct artificial respiration improperly, apply as well to the Schafer and Holger Neilsen method. The airway is just as likely to become obstructed when the subject lies on his face—especially when pressure is applied to the back—and/or the arms are pulled up so that the shoulder girdle rises and falls. The jaw does not have to be pulled forward when the muscles are in spasm, for the spasm breaks when there is sufficient hypoxia, or the subject recovers. Even so, the nasal passage forms a satisfactory airway, especially when the head is positioned properly. I have become exhausted in a short period of time while practising the Schafer method on a man who was larger and more muscular than I am. (I have reached the age where I can only grow in girth!)

I have no argument with Dr. Grant regarding his remarks about the variety of airways and resuscitation equipment, but if a simple, safe piece of airway equipment were used by a group of people who were trained as well as the men from the Power Commission are, I would hazard the guess that more of their real victims would be saved by direct artificial respiration than by any of the manual methods.

May I therefore suggest to Dr. Grant that his men would be competent in dealing with a far wider area of suffocation accidents if they were trained in the proper performance of direct artificial respiration?

At our University, several of us have been studying the problem of teaching resuscitation methods and have been in consultation with those working on this problem in England, Denmark and the U.S.A. We all feel that the "big blow" may cause confusion initially, but only if many people study a confusing problem can a logical conclusion evolve. It is the opinion of many of us who are doing this work that only by training the public in the universally applicable methods and training the "specialists" in several methods, can more lives be saved from suffocation.

ALLEN B. DOBKIN, M.D.,
Associate Professor of Anæsthesia,
University Hospital,
Saskatoon, Sask.,
February 24, 1960.

FREEDOM AND FLUORIDATION

To the Editor:

Your correspondent, Dr. C. P. Harrison, in the November 1 issue of the Journal (81: 763, 1959) makes an eloquent appeal for the ethical implications of water fluoridation. He specifically invokes a thesis that "perfection of the person lies in his being free rather than free from dental caries". This suggests complete misunderstanding of the ideals of freedom and of respect for the individual which, I submit, motivate proponents of this public health measure just as much as the opponents.

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It is quite apparent that a substantial number of people are deeply concerned with ways and means of mitigating their "personal dental health misfortunes". Responsible members of the health professions have therefore endeavoured to interpret the value of various dental health measures, including fluoridation, designed to alleviate these conditions. It is now argued that we have no right to recommend and to seek public consent to fluoridation, great though the need may be, because this implies infringement of human liberty. In that event can the problem be solved in any other way? Evidence concerning alternatives to water fluoridation for individual administration leaves many questions unanswered and consequently labels these, for the time being, as speculative or prohibitive, or both. Measures directed to the alteration of dietary habits and improvement in the general practice of oral hygiene have not, in themselves, proved adequate to cope with such a far-reaching problem. Therefore, it is reasonable to conclude that we have no practical alternative to recommend at the present time. As Dr. G. W. Griffith recently observed (*Pub. Health*, 74: 27, 1959), "It is now, and is likely to be for many years to come, a case of water fluoridation or nothing." This leaves us with a very simple choice. Either we accept this harmless increment in daily fluoride intake, or everybody—those who care as well as those who don't care—is deprived of a benefit he might otherwise enjoy. It is not simply a question whether we have a right to ask people to agree but rather whether there remains any morally tenable grounds for withholding consent.

Dr. Harrison rightly suggests that "in order to be free we must accept certain restrictions". The price of social existence is to be measured in freedom. But freedom is not static. It is capable of growth, so that we may lose one freedom in order to gain a larger one. Surely the proposal to relinquish one freedom in order to gain a larger freedom—a freedom to enjoy better dental health—is not incompatible with the high ideals to which we all subscribe.

F. H. COMPTON, D.D.S., D.D.P.H.,
Director, Division of
Dental Services.

Department of Public Health,
City Hall Annex, 465 Bay St.,
Toronto 2, Ont.,
February 16, 1960.

OBITUARIES

DR. DANIEL NEIL CHISHOLM, aged 65, of Port Hawkesbury, N.S., died at St. Martha's Hospital, Antigonish, on February 10. He was born at Port Hastings, the son of the late John B. and Sarah O'Brien Chisholm. He served overseas in the First World War and later graduated in medicine from McGill University and the University of Edinburgh, Scotland. He took postgraduate research at the Queens Research Institute in New York. On the death of his brother, Dr. Alex N. Chisholm, in 1937, he went to Port Hawkesbury to take over his practice.

Dr. Chisholm was active on the Board of Trade and was medical health officer for Port Hawkesbury. He is survived by his widow, the former Sarah Chisholm of Port Hawkesbury, a son, a sister and a brother.

W.K.H.

DR. DOROTHY M. JAMES, 50, died at her Toronto home on January 22. She had been ill for several months. Born in Bowmanville, Ont., she received her medical education at the University of Toronto, where she graduated in 1933. After graduating, she interned at the Hospital for Sick Children, Toronto, and then did postgraduate work in Birmingham, England, and in Philadelphia, specializing in pædiatrics. On her return to Canada, Dr. James started a practice in Toronto. In 1941 she was appointed medical adviser to the Infants' Home, Toronto, and when this organization was amalgamated with the Children's Aid Society in 1951, Dr. James became physician in charge of medical services to the Society.

DR. WILFRED LAISHLEY, 59, died at his home in Nelson, B.C., on January 2. He had been ill for some time. A native of Ottawa, Dr. Laishley graduated in medicine from McGill University in 1922. He did postgraduate work in New York, at the University of Southern California and at the Johns Hopkins Medical Center in Baltimore, specializing in otolaryngology.

His widow, a son and a daughter survive him.

DR. CONNOLLY J. MALLOY

AN APPRECIATION

Dr. Connolly J. Malloy died suddenly in Montreal on February 1, 1960, at the age of 55. His unexpected death, which occurred after a brief illness, came as a shock to his many patients and friends, and as a sad loss to his colleagues. Dr. Malloy studied at McGill University, obtaining his B.A. and later his M.D. in 1935. He interned at the Royal Victoria Hospital and the Children's Memorial Hospital in Montreal and served in the Canadian Army during World War II. At the time of his death he was an assistant physician at the Royal Victoria Hospital and lecturer in medicine at McGill University. He was a Fellow of the Royal College of Physicians, the American Academy of Allergy, the American College of Allergy, the International Association of Allergology and the American College of Physicians, and a member of the New York Academy of Sciences and of the American Association for the Advancement of Science. He took an active interest in the Canadian Academy of Allergy and was instrumental in the founding of the Association of Allergists of the Province of Quebec, of which he was vice-president. He had a scholarly knowledge of the classics, which was reflected in his publications. Always genial, he had a ready smile, a pleasant manner, and the mark of a gentleman.

Dr. Malloy is survived by his widow Helga, and his three children Brenda, Kirsten, and Brian.

BRAM ROSE

DR. DAVID B. MORRIS, 47, died at his home in Windsor, N.S., on January 11. Born in Windsor, he attended Dalhousie University and graduated in medicine in 1937. For the next three years Dr. Morris did postgraduate work in London, England, and in New York. He returned to Windsor in 1940 and went into practice with his father. In World War II, Dr. Morris served abroad with the R.C.A.M.C., returning to his Windsor practice in 1944.

He is survived by his widow and a son.

DR. F. D. O'CONNOR, 71, of Kingston, Ont., died on January 9 while on vacation in Florida. He took his medical studies at Queen's University and graduated in 1914. After graduation he began a practice in Tamworth, Ont. In 1935, Dr. O'Connor moved to Kingston where he later became chief of staff at the Hôtel-Dieu Hospital and also served on the city's board of health from 1940 to 1944.

He is survived by his widow, two daughters and one son, Dr. L. N. O'Connor.

DR. ARCHIBALD J. STEWART, 74, of Montreal, died suddenly in Ottawa on January 18. Born in Vankleek Hill, Ont., he studied medicine at McGill University, where he graduated in 1910. After graduating, he interned at the Royal Victoria Hospital, Montreal. In 1914 Dr. Stewart joined the staff of the Montreal General Hospital and became a lecturer at McGill. He went to England in 1922 and began postgraduate work in surgery at the London University. On his return to Canada, Dr. Stewart became an assistant in surgery at the Montreal General Hospital, and in 1938 he was appointed attending surgeon there. In 1942 he became assistant professor of surgery at McGill University and in 1950 he was made consultant in surgery at the Montreal General. He retired in 1955.

His widow survives him.

LE DR PIERRE VANDANDAIGUE est décédé le 29 février à l'âge de 88 ans. Il avait fait ses études à St-Hyacinthe et à l'Université Laval (Montréal) où il fut reçu en médecine en 1896. Après avoir complété ses études à Paris il exerça sa profession surtout à Verdun. Le Dr Vandandaigue fut l'un des fondateurs de l'Hôpital Général de Verdun. Il fut aussi médecin des écoles pendant près de 20 ans. Son épouse née Ann Elizabeth McCarthy lui survit.

PROVINCIAL NEWS

SASKATCHEWAN

The present status of the dental profession in Saskatchewan came under sharp criticism at a meeting of the Saskatoon and District Dental Society, when the feeling was expressed that the present Act will definitely undermine professional health services in dentistry in Saskatchewan, and deter new graduates from establishing practices in this province.

It was stated that the number of dentists has been declining in Saskatchewan until at present there are only 192 practising dentists. Since an amended Dental Act went into force on June 1, nine dentists have left the province, and a number of these stated that their decision to leave was definitely influenced by the Dental Act amendments.

According to a recent announcement by Premier Douglas, the Government of Saskatchewan will present advanced legislation for the Government's projected medical services plan at the forthcoming session of the Legislature. This legislation will give the Province authority to proceed with a plan and will form the basis of establishing a committee to study the project. According to Mr. Douglas, specific legislation on a medical plan would not be possible until a special committee the Government is setting up presents a report.

When the Premier was asked why the Government has decided not to put the medical plan before the voters in a plebiscite, he replied that "Our plebiscite will consist of going before the people of the province with the plan in the provincial election. If you want the plan, you vote for it; if you don't want it, you vote against us."

Dr. Peter White of Rosewell Park Memorial Institute, Buffalo, spoke at the University of Saskatchewan during January on "Biochemical mechanisms of drug resistance".

The Board of Governors of the City Hospital in Saskatoon has agreed to call for tenders on the first and major portion of an overall $220,000 renovation program. The first stage of the program calls for the complete rebuilding of the interior of the north end of the hospital's west wing. Further work is planned for the hospital's east wing.

St. Joseph's Hospital Advisory Board (Estevan) is requesting permission to construct a 60-bed addition. The 25-bed addition in 1956 brought the hospital's capacity at that time up to 75 beds.

Saskatchewan's hospitalization fund ran a deficit of $5,539,000, in the year ended December 31, 1958.

Statements of public accounts issued recently show that the fund collected $7,025,000 from its share of the hospitalization and education tax, $11,189,000 from personal hospital taxes, and $9,728,000 from general provincial revenues.

Total expenses for the year were $28,438,000 plus a deficit carry-over of $5,043,000 from the previous year.

Payment to general hospitals for in-patient services amounted to $26,427,000. Geriatric centres took $459,000 and out-patient services $87,000.

The first conference on Mental Retardation and annual meeting of the Saskatchewan Association for Retarded Children was held in Saskatoon on March 3 and 4.

Among the speakers were Dr. S. Kirk, Director, Institute of Research on Exceptional Children, University of Illinois; Dr. J. Gerrard, Professor of Pædiatrics, University of Saskatchewan; Dr. A. E. Buckwold, Medical Director of the Saskatchewan Council for Crippled Children and Adults; Dr. W. E. McNeill, Professor of Special Education, University of Saskatchewan; Dr. A. J. Beddie, Superintendent, Saskatchewan Training School; Dr. A. Stephen, Director of the McNeill Clinic for Psychiatric Services, Saskatoon; Dr. A. Roeher, Co-ordinator of Rehabilitation, Department of Public Health and Welfare; and Dr. Julian D. Levinson, Research Foundation for Mentally Retarded Children.

G. W. PEACOCK

Faculty changes in the College of Medicine, University of Saskatchewan, during the past year have been as follows: Dr. William Feindel and Dr. J. Olszewski left for professorial posts in neurosurgery and neuropathology respectively at the universities of McGill and Toronto. Dr. J. G. Stratford now heads

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neurosurgery and Dr. D. Baxter is in charge of both teaching and service in neuropathology. Dr. J. A. P. Cameron, assistant clinical professor of surgery and head of orthopædic surgery, has resigned to take up work in Great Britain. Dr. M. G. Kunkel has been appointed to succeed him.

New assistant professors are Dr. R. F. Badgley, M.A. (McGill), M.A., Ph.D. (Yale), medical sociologist, in the department of social and preventive medicine; and R. N. Beck, M.B., B.A.O., B.Ch., M.D. (Queen's, Belfast), M.R.C.P.(E.), in the department of medicine and in charge of the new metabolic laboratory in the University Hospital. Dr. Kenneth W. E. Paine, M.R.C.S. (Eng.), L.R.C.P.(Lond.), M.B., B.S.(Lond.), F.R.C.S. (Eng.), has come as a new full-time lecturer in surgery (Neurosurgery). Dr. E. M. Ashenhurst, M.B., B.Ch., M.R.C.P.(Edin.), was appointed instructor in medicine (Neurology) and A. M. Keil, M.A.(Cantab.), M.B., B.Chir., F.F.A.R.C.S., instructor in anæsthesia.

MANITOBA

Last year Dr. Paul B. Hagen was appointed professor of biochemistry and head of the department in the University of Manitoba. Dr. Hagen came to the University from Harvard Medical School, where he was assistant professor of pharmacology.

ONTARIO

Appointments in the Faculty of Medicine of the University of Western Ontario have included the following: Dr. M. S. Smout, assistant professor of pathology, effective July 1, 1959; Dr. W. C. C. McMurray, assistant professor of biochemistry, effective August 1, 1959; Dr. G. H. Valentine, assistant professor of pædiatrics (full-time geographic appointment), effective September 1, 1959; and Dr. R. Malone, assistant professor of pathology (St. Joseph's Hospital), effective September 21, 1959. Dr. J. A. Blezard, professor and head of the department of anæsthesia, retired on July 17, 1959, and has been succeeded as Head by Dr. W. E. G. A. Spoerel.

QUEBEC

The last meeting of the Medico-Chirurgical Society took the form of "Past Presidents' Night". This was held on February 15 with a scientific program preceded by the Past Presidents' Night dinner at the University Club. Twelve past presidents were able to attend and a total of 60 joined them to honour the past presidents. At 8.30 p.m. the scientific sessions were held in the auditorium of the Queen Mary Veterans Hospital with Dr. E. G. D. Murray, past president of 1942 and now living in London, Ontario, acting as the chairman. The guest speaker was Dr. Frank L. Horsfall, Jr., Vice-president for Clinical Studies, The Rockefeller Institute, and physician-in-chief of the Hospital of the Rockefeller Institute in New York. He spoke of virus infections of the respiratory tract. Because of the unique mechanism of the intracellular multiplication of viruses and its effect on cell biosynthesis, it is surprising that the episodes of illness which viruses induce usually terminate in recovery. The hypotheses put forward for this very frequent recovery are the development of specific antibodies, elimination of competent host cells, alterations in the environment of infected cells and changes in the products of viral reproduction. Dr. Horsfall then proceeded to prove that none of these mechanisms actually provide an adequate basis for this well-known recovery. Therefore, a concept that can unify the known facts requires the assumption that more than a single mechanism is operative in recovery from most viral diseases. It was a pleasure to note that some 250 members and guests attended this meeting.

Early in February the Fraser Research Laboratories, named in memory of Dr. John R. Fraser who served the Royal Victoria Hospital as gynæcologist-in-chief from 1929 to 1945, were officially opened by Mrs. Fraser at the Royal Victoria Hospital in Montreal. These new laboratories, located in the Women's Pavilion, have been made possible through donations from private sources and from the proceeds of the Hellenic Festival sponsored by the Greek community in September 1958. The equipment has been provided mainly through research grants from the provincial and federal health departments. Dr. George B. Maughan, gynæcologist-in-chief of the hospital, spoke briefly and paid particular tribute to the work of the late Dr. Fraser who, in addition to his other responsibilities, was also professor and chairman of the Department of Obstetrics and Gynæcology of McGill University and Dean of Medicine from 1942 to 1944. Under his leadership the clinical care of patients reached a peak second to none. He always pleaded for more basic research to achieve an understanding of the normal and abnormal birth processes.

Many of our colleagues took an active part in special promotional schemes during National Health Week in Canada. The number is too great for individual comment, but mention should be made of the special effort that was planned and directed by our Committee on Public Relations under the chairmanship of Dr. Thomas Hale.

The Montreal General Hospital has announced the promotion of Dr. E. F. Crutchlow from senior associate radiologist to the newly established post of senior radiologist, and of Dr. T. E. Dancey from associate psychiatrist to the newly created post of senior psychiatrist. Congratulations and best wishes to both.

A. H. NEUFELD

Le Préceptorat en Médecine Générale

La Faculté de Médecine de l'Université de Montréal est à instituer un programme de préceptorat à l'usage des étudiants de troisième année et auquel les omnipraticiens de la province sont invités à participer. Ce programme doit permettre aux élèves de saisir la portée de la pratique générale en suivant un médecin dans l'exercice de sa profession. Il pénètreront dans les foyers aux côtés du médecin de famille et apprendront à connaître non seulement les toutes premières manifestations de la maladie mais aussi l'influence que peuvent exercer dans ces circonstances le milieu familial, les croyances religieuses, la classe sociale et les conditions économiques. Les médecins auront la satisfaction de transmettre leur expérience à des jeunes gens désireux de se perfectionner et de perpétuer ainsi la tradition de l'omnipraticien en province de Québec. La fin de l'été semble la période de l'année la plus propice à la mise en œuvre de ce programme. Les autorités de la

Faculté espèrent que les réponses à cette invitation seront nombreuses tant de la part des élèves que de celle des médecins. Les praticiens des milieux ruraux sont spécialement désignés pour participer à cette initiative par laquelle ils pourront démontrer la nécessité de leur apport à la formation des étudiants en médecine. Tous les médecins que ce programme pourrait intéresser, sont requis de communiquer avec le docteur J. G. Bonnier, aux soins de la Faculté de Médecine de l'Université de Montréal, 2900 boul. du Mont Royal, Montréal, P.Q.

NEW BRUNSWICK

Dr. Paul Carette of Campbellton has been appointed by the Provincial Government of New Brunswick to the Board of New Brunswick Development Corporation, the new provincial crown agency aimed at promoting industry.

Dr. Kenneth C. Rodger, internist of Saint John, addressed Medical Societies at Woodstock and Edmundston on January 26 and 27 on "The use and abuse of antibiotics". At both centres clinical presentations and discussions by local doctors were a feature. Dr. Fred Whitehead, secretary of the New Brunswick Medical Society, introduced new business and topics of economic interest at the luncheons and discussion periods. Dalhousie University and the New Brunswick Medical Society co-operated with the Bingham Associates Fund in sponsoring these extramural meetings.

Dr. W. A. Cochrane, professor of pædiatrics, Dalhousie University, visited Moncton Medical Society on January 28 and joined local doctors at a clinical session at the Moncton City Hospital in the afternoon and at dinner in the evening. He gave a paper on non-tuberculous respiratory infection in children.

Dr. D. A. Thompson of Bathurst was installed as president of the Royal College of Physicians and Surgeons of Canada for 1960-61 at the annual meeting of the College held in Montreal. Dr. Thompson has served his profession in many capacities and has held many offices in medical organizations and community affairs. New Brunswick is proud to congratulate this Maritime doctor on his latest honour.

Dr. Finlay McKerracher has been appointed hospital administrative consultant on the staff of the hospital services commission of New Brunswick. Previous to this appointment he was assistant superintendent of the General Hospital at St. John's, Newfoundland.

Dr. A. S. Cowie of Fredericton is now medical officer in charge of medical assessment of hospital claims.

Dr. Thomas Nugent of Bath, N.B., has received the Distinguished Service Medallion from the Canadian Red Cross Society in recognition of his work for the blood donor service.

Dr. Fred Whitehead, secretary of the New Brunswick Medical Society, representing the Post-Graduate Department of Dalhousie University and the New Brunswick Medical Society, arranged two successful extramural meetings in Saint Stephen and Saint John on February 17 and 18, addressed by Dr. Lea C. Steeves, associate professor of medicine and Director of the Division of Post-Graduate Medicine at Dalhousie University. His subject at both meetings was the management of cardiac emergencies. The meeting at Saint John was the regular February meeting combining business and the pleasure of listening to our guest from Halifax. In Saint Stephen the afternoon session was held in the Charlotte County Memorial Hospital and the evening dinner session was enjoyed in Calais, Maine.

Dr. J. Cyril Sinnott, internist of Charlottetown, P.E.I., and Gold Medallist, Division of Medicine, at the recent annual meeting of the Royal College of Physicians and Surgeons of Canada, presented a paper on the control of pulmonary ventilation before the Medical Society of Moncton and District on February 18. All Maritime doctors congratulate Dr. Sinnott on his well-deserved distinction.

Dr. Charles W. Kelly of the Department of Health and Social Services of New Brunswick had the misfortune to fall and fracture his thigh during our early Maritime winter.

Dr. E. A. Petrie, director of the department of radiology at St. Joseph's Hospital, Saint John, has been appointed to the Board of Chancellors of the American College of Radiology, representing Canada. Dr. Petrie has been a Fellow of the College for several years and counsellor for the Maritimes.

A. S. KIRKLAND, M.D.

ABSTRACTS *from current literature*

MEDICINE

P-Wave Morphology in Precordial Lead V_1 in Patients with Elevated Left Atrial Pressures and Left Atrial Enlargement.

D. S. DINES AND T. W. PARKIN: *Proc. Staff Meet. Mayo Clin.*, 34: 401, 1959.

It is well known that changes in the morphology and electrical axis of the P waves of the electrocardiogram may occur as a consequence of enlargement or hypertrophy of the right or left atrium or a combination of one or all of these factors. Perhaps the best-known changes are those in the standard leads. It is recognized that abnormalities of the P wave in the precordial leads also may occur, but the literature contains few articles pertaining to the specific changes which occur and the incidence of such changes. In experience with patients who had chronic rheumatic valve disease, the writers noted frequently that the P wave in precordial lead V_1 appeared to be diphasic (plus-minus type) and that the negative portion of this deflection appeared to be unusually broad and deep. They decided therefore to study a series of electrocardiograms of patients with known enlargement of the left atrium to determine the type and incidence of abnormalities of the P wave in precordial lead V_1.

Firstly, the morphology of the P wave in right precordial lead V_1 of the electrocardiograms of 50 persons

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with a normal heart was studied. A diphasic (plus-minus type) pattern was noted in 25 (50%) tracings. The range of depth of the negative portion of this wave was 0.5 to 1.5 mm. (mean 0.80 mm.) and the mean duration of the entire P wave was 0.07 second. Next, the P wave was studied in the right precordial lead V_1 of the electrocardiograms of 31 patients with higher than normal pressures in the left atrium, as determined by cardiac catheterization and with radiological evidence of left atrial enlargement. Twenty-seven (87%) of these patients exhibited a type of diphasic (plus-minus type) P wave in which the negative portion of deflection was broad and deep. The depth of the negative deflection ranged from 0.5 to 3.5 mm. with a mean of 2.55 mm. The total mean duration of the entire P wave was 0.12 second.

It would thus appear that an increase in breadth and depth of the negative portion of the diphasic T wave is a common finding in left atrial disease. S. J. SHANE

Hæmodynamic Sequelæ of Sustained Elevation of Left Atrial Pressure.

A. SELZER: *Circulation*, 20: 243, 1959.

A series of 98 patients, 63 with mitral stenosis and 35 with chronic left ventricular failure, underwent cardiac catheterization, for comparison of hæmodynamic findings in these two conditions. The mitral stenosis and the left ventricular failure were graded as to severity by the use of the index:

$$\frac{\text{Cardiac output}}{\text{Left atrial pressure}} \times 100$$

The hæmodynamic sequelæ of the sustained elevation of the left atrial pressure, which occurs in both disease states, showed important similarities and minor differences. In both groups, the pulmonary artery pressure is always elevated, but in many cases the pulmonary hypertension is out of proportion to the left atrial hypertension, signifying an abnormally high pulmonary vascular resistance. In both conditions, the resting cardiac output was, on the average, abnormally low in severe cases and normal or slightly reduced in milder cases. Inadequate rise of cardiac output with exercise was frequently observed in both groups.

From these and other findings, it is concluded that mitral stenosis does not have a distinctive hæmodynamic pattern that would permit a distinction between a "mechanical block" and a "myocardial factor" unless direct measurement of left atrial and left ventricular pressure permits the demonstration of a diastolic gradient across the mitral valve. S. J. SHANE

Cardiac Enlargement due to Myocardial Degeneration of Unknown Cause: Effect of Prolonged Bed Rest.

G. E. BURCH AND J. J. WALSH: *J. A. M. A.*, 172: 207, 1960.

Case reports of five patients are presented whose cardiac enlargement of unknown origin failed to respond to conventional therapy until prolonged bed rest was instituted. The authors believe that the process from which these patients suffered was not rheumatic. Each had cardiomegaly, a low pulse pressure and increased sensitivity to digitalis-like preparations. In contrast to the acute transitory cardiomegaly of initial heart failure, these patients showed marked persistent enlargement of the heart, and its reduction was very slow and was produced only after prolonged bed rest. The danger of persistent cardiomegaly in patients and the desirability of complete restoration of the heart to normal size as evidence of complete cure are stressed.

The authors emphasize the need for strict bed rest for periods up to one year or longer in some cases of non-rheumatic myocarditis. W. GROBIN

Bone Marrow Needle Biopsy.

J. I. BRODY AND S. C. FINCH: *Am. J. M. Sc.*, 238: 140, 1959.

The results obtained with a bedside Vim-Silverman bone marrow biopsy technique on 20 patients are reported in this paper. The method has been found particularly useful in instances where bone marrow sampling by means of aspiration has been inadequate. The method is recommended as being simple, safe, convenient for the patient, and entirely adequate for diagnosis. It is believed that this method will supplant the use of a surgical trephine procedure for biopsy of the bone marrow in most instances. S. J. SHANE

SURGERY

Resection of the Pre-aortic Plexus by the Method of Arnulf: Palliative Treatment of Angina Pectoris.

I. GREWALD: *Acta chir. scandinav.*, 117: 351, 1959.

The author describes 52 patients with angina pectoris, who underwent operation by the method of Arnulf. This operation involves resection of the nerves constituting the pre-aortic plexus under local anæsthesia. [This plexus, incidentally, is not mentioned in any of the standard anatomy texts—Grey, Cunningham, Grant, Morris, Callander, Lee McGregor.] The pre-aortic plexus supposedly supplies the coronary vessels with sensory, sympathetic and vaso-constrictive fibres.

The difficulty of defining angina pectoris is discussed. In only three cases were the patients relieved of their angina. Approximately one-third had good relief of pain; one-third had some relief of pain, and one-third had no relief.

There were 19 complications and two of these led to the death of the patients. Ten of the cases became infected. [It seems extraordinary to have an infection rate of almost 20% in a "clean" operation in the chest.] T. A. MCLENNAN

Anastomosis of Vena Cava and Pulmonary Artery.

P. W. SANGER, F. ROBICSEK AND F. H. TAYLOR: *J. Thorac. Cardiovasc. Surg.*, 38: 166, 1959.

The superior vena cava and pulmonary artery were anastomosed in an 11-year-old boy who had complete transposition of the great vessels, interatrial septal defect and pulmonic stenosis. In the course of the operation, the superior vena cava and right pulmonary artery were ligated proximally and cross-sectioned, and an end-to-end anastomosis was performed between the distal stumps of the vessels. In this way about 50% of the systemic venous blood flow by-passed the right heart and became shunted directly into the right lung. The patient tolerated the procedure well and improved significantly postoperatively.

The procedure is recommended for the treatment of congenital heart disease when pulmonary blood flow is impaired, pulmonary vascular resistance is not elevated, and complete surgical repair cannot be performed because of anatomical reasons or because of the patient's age or general condition. This group would include tricuspid atresia and stenosis, hypoplasia of the right ventricle, atresia of the pulmonary artery, and certain forms of tetralogy of Fallot. S. J. SHANE

Myxoma of the Lung.

J. B. LITTLEFIELD AND E. C. DRASH: *J. Thoracic Surg.*, 37: 745, 1959.

A primary myxoma of the lung was successfully treated by resection without evidence of recurrence after 28 months. Only one other similar lesion has been previously reported in the literature. Myxoma of the lung exhibits the same histological appearance and biological behaviour as myxomas originating elsewhere in the body.

Myxomas are best defined by strict histological criteria which include their characteristic stellate cells and prominent intercellular mucinous stroma, and would exclude tumours composed primarily of other tissue elements. Myxoma is basically a benign tumour with a tendency to repeated local recurrence. Biopsy of a suspected mesenchymal tumour should be performed whenever possible before beginning treatment. Experience with extrapulmonary myxomas demonstrates that successful treatment depends upon a wide surgical excision; initially radiation therapy is of limited usefulness. S. J. SHANE

Experimental Studies of Factors Influencing Hepatic Metastases.

B. FISHER AND E. R. FISHER: *Ann. Surg.*, 150: 731, 1959.

The effect of surgical trauma with special reference to liver injury was studied in rats, using the Walker 256 carcinosarcoma. The incidence of liver metastases after injection of a standard dose of tumour cells was 20% after two weeks and 20% after eight weeks. But if the liver was manipulated at operation at 14 days, there were metastases in 84% at 21 days. Other traumata, such as dorsal incisions, injection of air into the peritoneum, ether anæsthesia or laparotomy, did not increase liver metastases. Partial hepatectomy increased the "take" to 64%, as did sham hepatectomy and chloroform injection to cause ventral necrosis. The same result followed similar procedures in adrenalectomized rats, so it was not likely that "stress" was an influence. Repeated liver trauma increased the appearance of hepatic metastases in 100% of the animals. It appears that "dormant" tumour cells were thus stimulated to become active. BURNS PLEWES

Vascular Complications of Cervical Rib.

J. P. Ross: *Ann. Surg.*, 150: 340, 1959.

Compression of the subclavian artery by a cervical rib causes intermittent forearm pain, pallor of the hand when raised and blueness when dependent, paræsthesia, coldness and sometimes ulceration of the fingers. These clinical features indicate embolic occlusion of the main arteries of the upper limb and arteriography confirms this. The cervical rib under these circumstances is a complete one, forming a diarthrodial joint with the first rib. This prominence indents the subclavian artery, producing stenosis with dilatation distal to it. Emboli originate from the clot formed in the turbulent blood stream in the dilated portion. A complete cervical rib does not compress the brachial plexus.

Treatment is by excision of the cervical rib and the hyperostosis on the first thoracic rib and an upper thoracic sympathectomy. The subclavian artery should not be excised. BURNS PLEWES

Late Results of Treatment of Abdominal Aortic Aneurysm by Replacement with Aortic Homograft.

L. O. SHERANIAN, J. E. EDWARDS AND J. W. KIRKLIN: *Surg. Gynec. & Obst.*, 109: 309, 1959.

The overall three-year survival rate in 110 cases treated for abdominal aortic aneurysm by homografting at the Mayo Clinic is 70.7%. This compares to DeBakey's survival rate of 69% (in 230 cases) for the same period of time. In Estes's series (of 102 cases) the three-year survival rate of untreated aortic aneurysms was 49.2%. However, the high percentage of ruptures of the homograft (both early and late) has prompted a change to synthetic grafts at the Mayo Clinic. The conclusion is reached that the survival rate of patients with abdominal aortic aneurysms treated by resection and homografting is better than that of untreated patients. T. A. MCLENNAN

Acute Obstructive Cholangitis.

B. M. REYNOLDS AND E. L. DARGAN: *Ann. Surg.*, 150: 299, 1959.

Acute obstructive cholangitis, a distinct clinical syndrome which is properly treated by emergency operative drainage, is illustrated by four case reports. Chills and fever, jaundice and right upper quadrant pain and tenderness indicate cholangitis. The addition of lethargy or mental confusion and shock represents acute obstructive cholangitis. Early surgical decompression is ideal treatment. Acute obstructive cholangitis quickly leads to shock and operative intervention is mandatory in spite of the patient's poor condition. Drainage of the common duct and removal of the stone lead to immediate and dramatic improvement. Hepatic insufficiency and sepsis together quickly produce an apparently moribund state. BURNS PLEWES

THERAPEUTICS

Dangers of Prolonged Anticoagulant Therapy in Hepatic Disease.

W. F. KLIESCH, P. C. YOUNG AND W. E. DAVIS, JR.: *J. A. M. A.*, 172: 223, 1960.

A 54-year-old man, who had been taking 50 mg. of phenindione twice daily since a myocardial infarction four years previously, was admitted to hospital with jaundice and with hæmorrhagic manifestations. There was both a personal and a family history of alcoholism. The clinical impression that the patient was suffering from viral hepatitis and hypoprothrombinæmia, secondary to prolonged anticoagulant therapy, was later confirmed by needle biopsy of the liver. The acute changes of hepatitis were found to subside on repeat biopsy at a later date, but early cirrhosis of the liver became obvious at this time.

The dangers of intercurrent hepatitis during anticoagulant therapy are stressed. Widespread liver damage potentiates the effect of anticoagulant therapy. W. GROBIN

Use of Mechanical Assistance in Treating Cardiopulmonary Diseases.

F. D. GRAY, JR. AND A. S. FIELD, JR.: *Am. J. M. Sc.*, 238: 146, 1959.

A rhythmically inflated abdominal belt functioning alternately with mouth-inspiratory positive pressure was used as a method for ventilating patients with severe pulmonary emphysema. It helps reduce overdistension,

lowers alveolar carbon dioxide tension, and maintains blood pressure in cases of vasomotor instability. An apparatus providing alternate and rhythmic electric neuromuscular stimulation of the diaphragm and lower abdominal muscles also provides adequate ventilation in emphysematous patients. The authors feel that it shows promise as an instrument useful in initiating diaphragmatic breathing exercises in those patients who have impaired diaphragmatic motion.

S. J. SHANE

Isoniazid and Para-Aminosalicylic Acid Toxicity in 513 Cases.

S. J. BERTE AND H. J. DEWLETT: *Dis. Chest*, 36: 146, 1959.

These authors review toxic drug reactions in 513 patients receiving isoniazid and 303 patients receiving PAS. Sixty-nine per cent were observed for three months. All had received at least one month of therapy at the time of this study. Out of 303 patients taking PAS, drug allergy and gastro-intestinal intolerance occurred in 8.9%. Only 4.9% developed gastro-intestinal symptoms, e.g. nausea, vomiting, and diarrhœa. Only 0.97% of the 513 patients receiving isoniazid developed toxic symptoms. Toxic reactions that did occur were among the 329 patients taking high doses of isoniazid. The percentage toxicity from isoniazid in these 329 cases was 1.52%. By using the methods described in detail, the authors believe that high doses of isoniazid plus PAS can be safely given to large numbers of tuberculosis patients for prolonged periods, provided these patients are otherwise in a state of good nutrition and do not have pre-existing disease of the central nervous system or liver.

S. J. SHANE

FORTHCOMING MEETINGS

CANADA

CANADIAN ANÆSTHETISTS' SOCIETY, Western Divisional Meeting, Victoria, B.C. (Dr. W. L. Esdale, Secretary-Treasurer, B.C. Division, Canadian Anæsthetists' Society, 7476 Inverness St., Vancouver.) April 28-30, 1960.

QUEBEC DIVISION, Canadian Medical Association, 22nd Annual Meeting, Quebec City. (Dr. D. G. Kinnear, Honorary Secretary, 2115 Drummond Street, Montreal 25, Que.) May 5-7, 1960.

DIVISION DU QUÉBEC, Association Médicale Canadienne. Le 22e congrès annuel sera tenu dans la ville de Québec. (Dr D. G. Kinnear, secrétaire honoraire, 2115 rue Drummond, Montréal 25e.) 5-7 mai 1960.

ONTARIO MEDICAL ASSOCIATION, 80th Annual Meeting, Toronto, Ont. (Dr. Glenn Sawyer, General Secretary, 244 St. George Street, Toronto 5, Ont.) May 9-13, 1960.

CANADIAN ACADEMY OF ALLERGY, Annual Meeting, Victoria Hospital, London, Ont. (Dr. John H. Toogood, Secretary, 450 Central Ave., London, Ont.) May 14, 1960.

CANADIAN PUBLIC HEALTH ASSOCIATION, 48th Annual Meeting, Halifax, N.S. (Dr. G. W. O. Moss, Honorary Secretary, 150 College Street, Toronto 5, Ont.) May 31-June 2, 1960.

CANADIAN FEDERATION OF BIOLOGICAL SOCIETIES (comprising the Canadian Physiological Society, the Pharmacological Society of Canada, the Canadian Association of Anatomists and the Canadian Biochemical Society), Third Annual Meeting, Winnipeg, Man. (Dr. E. H. Bensley, Honorary Secretary, Montreal General Hospital, 1650 Cedar Ave., Montreal 25, Que.) June 8-10, 1960.

THE SOCIETY OF OBSTETRICIANS AND GYNÆCOLOGISTS OF CANADA, Annual Meeting, Jasper Park Lodge, Jasper, Alta. (Dr. F. P. McInnis, Secretary, 280 Bloor St. West, Toronto 5, Ont.) June 9-12, 1960.

CANADIAN OTOLARYNGOLOGICAL SOCIETY, (SOCIÉTÉ CANADIENNE D'OTOLARYNGOLOGIE), Annual Meeting, Jasper Park Lodge, Jasper National Park, Alberta. (Dr. Donald M. MacRae, Secretary, 324 Spring Garden Road, Halifax, N.S.) June 10-12, 1960.

CANADIAN MEDICAL ASSOCIATION, 93rd Annual Meeting, Banff, Alberta. (Dr. A. D. Kelly, General Secretary, C.M.A. House, 150 St. George Street, Toronto 5, Ont.) June 13-17, 1960.

CANADIAN DIETETIC ASSOCIATION, 25th National Congress, Montreal, Que. (Miss Claire Dalmé, M.N.S., Chairman, Publicity Committee, Institute of Dietetics and Nutrition, University of Montreal, P.O. Box 6128, Montreal, Que.) June 14-16, 1960.

CANADIAN TUBERCULOSIS ASSOCIATION, 60th Annual Meeting, Ottawa, Ont. (Dr. G. J. Wherrett, Executive Secretary, 265 Elgin St., Ottawa, Ont.) June 27-30, 1960.

CANADIAN UROLOGICAL ASSOCIATION, Annual Meeting, Banff Springs Hotel, Banff, Alta. (Dr. David Swartz, President, 332-404 Graham Ave., Winnipeg 1, Man.) July 1-3, 1960.

PACIFIC DERMATOLOGIC ASSOCIATION, Annual Meeting, Victoria, B.C. (Dr. Edward J. Ringrose, Secretary-Treasurer, 2636 Telegraph Ave., Berkeley 4, Cal., U.S.A.,) September 1-4, 1960.

2ND WORLD CONGRESS OF THE WORLD FEDERATION OF SOCIETIES OF ANÆSTHESIOLOGISTS, Toronto, Ont. (Dr. R. A. Gordon, Chairman of Organizing Committee, 178 St. George Street, Toronto 5, Ont.) September 4-10, 1960.

CANADIAN HEART ASSOCIATION AND NATIONAL HEART FOUNDATION OF CANADA, Joint Annual Meeting, Toronto, Ont. (For information write: Dr. John B. Armstrong, National Heart Foundation, 501 Yonge St., Toronto 5, Ont.) November 30 to December 3, 1960.

UNITED STATES

7TH INTERNATIONAL ANATOMICAL CONGRESS, New York. (Dr. D. W. Fawcett, Executive Secretary, Department of Anatomy, Cornell University Medical College, 1300 York Ave., New York 21, N.Y.) April 11-16, 1960.

SOCIETY OF AMERICAN BACTERIOLOGISTS, 60th Annual Meeting, Philadelphia, Pa. May 1-5, 1960.

NATIONAL TUBERCULOSIS ASSOCIATION, Annual Meeting, in conjunction with the American Trudeau Society, Los Angeles, Calif. (Sol S. Lifson, Director, Education and Public Relations, National Tuberculosis Association, 1790 Broadway, New York 19, N.Y.) May 16-18, 1960.

INTER-SOCIETY CYTOLOGY COUNCIL, Annual Scientific Meeting, Chicago, Ill. (Dr. Paul A. Younge, Secretary-Treasurer, 1101 Beacon St., Brookline 46, Mass.) September 23-25, 1960.

AMERICAN COLLEGE OF SURGEONS, 46th Annual Clinical Congress, Son Francisco, Cal. (Dr. William E. Adams, Secretary, American College of Surgeons, 40 East Erie St., Chicago 11, Ill.) October 10-14, 1960.

OTHER COUNTRIES

Second Asian-Pacific Congress of Cardiology, Melbourne, Australia. (Dr. A. E. Doyle, Secretary, Alfred Hospital, Melbourne, S.1, Victoria, Australia.) Week of May 23, 1960.

VIII INTERNATIONAL CONGRESS OF HÆMATOLOGY, Tokyo, Japan. (Organizing Committee, Science Council of Japan, Ueno Park, Taito-ku, Tokyo, Japan.) September 4-10, 1960.

BOOK REVIEWS

THE REWARDS OF MEDICINE. Hugh Barber. 140 pp. H. K. Lewis & Co. Ltd., London, 1959. 15 shillings.

In view of the emphasis laid by our President on the need for the Canadian Medical Association to assist in a drive for physical fitness, it is ironical to find Dr. Barber in the present work quoting Gibbon to the effect that "the starving physicians of Arabia murmured a complaint that exercise and temperance deprived them of a greater part of their practice". This little volume of essays by an elderly English physician takes its name from the first essay on "The Rewards of Medicine". The whole series is full of random thoughts, pieces of wisdom, quotations from unusual sources and fragments of medical history. The essays, most of which are reprinted from *Guy's Hospital Gazette*, cover a very wide range of subjects including the teaching of medical history, the act of dying (a particularly commendable essay), good and bad fiction, spas, bodysnatchers, medicine in English literature, and some thoughts on old age. One of the little quotations which might be applied to medicine is that of the Victorian lady who said of Thomas Carlyle "on some things he thinks for himself and this is very wrong". This is an amusing and interesting book to dip into at odd moments; the browser through the pages of Dr. Barber's essays will also accumulate quite a few good thoughts and pieces of knowledge.

MODERN TRENDS IN ENDOCRINOLOGY. Edited by H. Gardiner-Hill, Consultant Physician to St. Thomas's Hospital, London, England. 298 pp. Illust. Butterworth & Co. (Canada) Ltd., Toronto, 1958. $13.00.

General physicians and endocrinologists would find this book worth their attention. The experts chosen by the editor have written with good judgment about their respective fields. The basic science and laboratory aspects of endocrine disease have been stressed. However, as one might expect from our British colleagues, the clinical features are also dealt with in sufficient detail to be of considerable help in the diagnosis and management of patients with major endocrine disorders.

Present knowledge of the thyroid hormone is covered in a very informative chapter written by Dr. Pitt-Rivers, who has contributed greatly to recent advances in thyroidology. The antithyroid drugs are discussed thoroughly by Prof. D. M. Dunlop of Edinburgh. Dr. J. C. Gilliland reviews the complicated subject of the etiology and treatment of exophthalmos in a clear and forthright manner. In the chapter on tests of thyroid function, the statement is made that the estimation of serum protein-bound iodine is too difficult a procedure to be used as a routine test. However, most workers in North America regard it as so valuable an index of thyroid function that every effort should be made to overcome these technical difficulties. The diagnostic and therapeutic uses of radioactive iodine are presented in separate sections. Detailed suggestions are given for the treatment with this agent of the rare cases of well-differentiated thyroid cancer.

An interesting chapter on the endocrine factors involved in the syndrome of diabetes mellitus, contributed by Dr. P. J. Randle, concludes with some stimulating suggestions for further research. The section on endocrine aspects of overnutrition and undernutrition by Drs. Kennedy and McCance also includes a discussion of hypothalamic control of the anterior pituitary gland. The diagnosis and treatment of diabetes insipidus is well covered in the chapter by Dr. Black on pituitary antidiuretic hormone and its relation to the control of fluid balance. Much space is devoted to the newer knowledge of adrenal steroids in physiology and therapeutics. The chapter on the pharmacology of the steroids is a worth-while addition in a volume dealing with endocrinology. Hormonal factors in lactation, mammary cancer and cancer of the prostate are discussed by authorities in these fields. The endocrine treatment of gynæcological disorders and methods of investigating infertility in the female are well reviewed. There is no chapter on infertility in the male. The discussion of carcinoid tumours and serotonin will help to uncover more cases of carcinoid syndrome.

The concluding chapter on the development of the stress concept and its significance in clinical medicine is mainly propaganda. The book would have lost nothing if it had been omitted.

HEAVY METALS AND THE BRAIN. John N. Cumings, Professor of Chemical Pathology, University of London, England. 161 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1959. $8.50.

Professor Cumings, well known for his work on Wilson's disease, has applied the same thoroughgoing scientific criteria to his compendium on copper, mercury and lead poisoning and its effects on the central nervous system. In his book of 160 pages nearly one-fifth is bibliography, with some 880 references, thus illustrating the extensive research he has done in order to write it.

Neurologists, pathologists, biochemists, and medical men in private or industrial medicine will find this volume of value and an excellent source of reference. In addition, medical historians would find it of interest since each section is preceded by the metal's history in producing disease.

The sections on pathology are perhaps most authoritative and detailed, and normal and abnormal biochemical data on each metal are similarly complete, with helpful tables within the text. The clinical picture is described somewhat and up-to-date treatment well, with perhaps a leaning towards the more successful and uncomplicated reports of attempted treatment with the newer drugs. The reader who intends to treat with the newer chelating agents will have to refer to recent publications on complications and mishaps, in particular with EDTA.

BIOCHEMICAL INVESTIGATIONS IN DIAGNOSIS AND TREATMENT. John D. N. Nabarro. 299 pp. Illust. 2nd ed. Little, Brown and Company, Boston; J. B. Lippincott Company, Montreal, 1958. $6.00.

The author states that no major changes have been made in this edition. A number of new sections have been added on such topics as abnormal hæmoglobins and the syndrome of malignant carcinoid; the section on the adrenal gland has been rewritten.

This short book is surprisingly complete and contains most of the facts necessary to a proper understanding of the common clinical metabolic disturbances.

The book fulfils its objective of serving as a practical guide for hospital resident staffs.

Canad. M. A. J.
April 9, 1960, vol. 82

RADIOGRAPHIC ATLAS OF SKELETAL DEVELOPMENT OF THE HAND AND WRIST. William Walter Greulich and S. Idell Pyle, Stanford University School of Medicine. 256 pp. Illust. 2nd ed. Stanford University Press, Stanford, Calif., 1959. $15.00.

Like their teacher, the late T. Wingate Todd, to whose memory this book is dedicated, the authors have long been interested in problems of growth. Requiring means of determining the physical developmental status of boys and girls, beyond those of *age, height* and *weight*, they turned to radiology and there found that *x-ray films* of the wrist and hand provided the most dependable index of the degree of maturity of the body.

After a project lasting many years, they were able to select from their thousands of films a consecutive series of standard films, spaced from six to 12 months apart: from birth to 19 (or 18) years of age there were 31 for boys, and 27 for girls.

The boys and girls, who were white and born in the United States, were taken not at random from the population at large but from families that were above the average economically and that promised co-operation until the completion of the project. This involved from two to 21 examinations for each child.

In essence, this book consists of a series of standard radiological plates to which clinicians and others may refer films of their young patients in order to determine whether they are normal for their age or retarded or advanced, that is to say, whether or not the chronological and skeletal ages coincide and, if not, by how much they differ. Photographs of retarded and advanced boys and girls, with accompanying radiographs, emphasize the wide significance of this matter in which the skeletal and reproductive systems are so closely related and where genetics and nutrition play their parts, as discussed lucidly in the text.

In this second and perfected edition—the plates have gained immensely in sharpness and in clarity through being re-made—the changing features, or progressive metamorphosis towards maturity, of each bone considered individually are indicated in line drawings much more effectively than before; tables for predicting adult stature from skeletal age are included; and the text has been enlarged in accordance with the increased experience of the authors.

CRANE ET FACE DANS LA MALADIE DE PAGET (Cranium and Face in Paget's Disease). J. A. Liévre and H. Fischgold. 131 pp. Illust. Masson et Cie, Paris, France, 1959. $10.00.

Ce travail est basé sur 75 dossiers choisis parmi 389 observations de maladie de Paget. Les auteurs ont tiré partie des techniques radiographiques modernes—agrandissements à foyer fin, tomographie, tirage au Logétron etc.

Bien que certaines théories pathogéniques et quelques symptômes cliniques soient mentionnés, le but de cette publication est une description radiologique détaillée et une évaluation toute particulière de l'évolution de l'ostéoporose circonscrite, que les auteurs démontrent être un stade de début de la maladie de Paget à manifestation crânienne. Cette étude est fondée entre autres sur 10 patients observés pendant des périodes variant de 9 mois à 11 ans.

La description de la texture osseuse tant dans l'ostéoporose circonscrite que les lésions classiques du Paget est particulièrement bien illustrée par la reproduction des images agrandies par foyer fin. Les auteurs établissent, surtout en ce qui a trait aux lésions élémentaires du Paget classique, une terminologie descriptive, imagée, mais significative. La différence entre impression basillaire et convexobasie est bien établie et un nouveau repère est décrit par l'un des auteurs pour reconnaître l'impression basillaire sur radiographie de face.

Un exercise radiologique intéressant serait de pouvoir graduer l'évolution pagétique au niveau du rocher comme les auteurs peuvent le faire. A noter cependant que leurs observations démontrent que le Paget ne débute pas à la base du crâne. Pour les auteurs, le *leontiasis ossea* est un syndrome dont la cause la plus fréquente est la maladie de Paget de la face.

Ce volume de 59 pages de texte, suivies de 75 pages de bonnes reproductions radiographiques est écrit spécialement pour des radiologistes et ne comporte pas de détails cliniques. Pour ceux que la maladie de Paget intéresse particulièrement, ce volume est un complément précieux.

DIE WIRBELSAULENLEIDEN UND IHRE DIFFERENTIALDIAGNOSE (Vertebral Lesions and Their Differential Diagnosis). J. E. W. Brocher, Geneva, Switzerland. 457 pp. Illust. 2nd ed. Georg Thieme Verlag, Stuttgart, W. Germany; Intercontinental Medical Book Corporation, New York, 1959. $30.50.

In recent years several voluminous essays have made their appearance on the theme of the vertebral column and its diseases, the most important being the work of the late G. Schmorl which treats the subject mostly from anatomo-pathological and macroradiological viewpoints. The work of Brocher deals mostly with clinical and macroradiological pictures of spine diseases. The author analyzes case histories and presents their pathological data as seen in macroradiographs. In spite of the title of his book, the writer does not limit himself to diagnosis but also discusses treatment. If the author's analysis of clinical and radiological data is accepted, his classification of diseases is obsolete. No one can speak seriously nowadays about "the degenerative diseases" when these "diseases" are the inevitable attributes of bone aging, just as the presence of the epiphysial centre of ossification is the attribute of growing bone. The writer himself points out that some authors have found signs of degeneration in the bones of a nine-year-old child. Thus, degeneration is neither a direct nor an indirect sign of spinal disease; it is a finding without clinical importance, especially in old age. It would be better if the book started with a description of normal findings typical for each age group, instead of describing borderline cases between the normal and pathological and only after that discussing spinal diseases. Without this introduction, the book fails to persuade and might confuse the unsophisticated student.

Illustrations, though technically good, are given as positive images which lose many details of x-ray absorption differences present in original negatives. The price is high, but the paper and type are excellent.

(Continued on advertising page 26)

OBSTETRICIAN-GYNÆCOLOGIST, Canadian, F.R.C.S.[C.]. Age 33. Interested in solo, association with another specialist, or group. Reply to Box 713, CMA Journal, 150 St. George St., Toronto 5, Ontario.

F.R.C.S.(E) married, one child, experienced general surgery and trauma, seeks post in Canada. Reply Fletcher, Addenbrooke's Hospital, Cambridge, England.

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WANTED IMMEDIATELY.—Orthopædic surgeon for two half-days per week for west Toronto clinic. Very interesting and lucrative orthopædic practice in association with 6 general practitioners and 10 specialists. Phone Mr. H. W. Jackson, CL. 5-1161.

PHYSICIAN required at a temporary town site serving an Ontario Hydro construction project in northern Ontario. Opportunity for a young doctor to gain experience and improve financial status before beginning his own practice or going into specialized studies. Attractive salary and other benefits. Commencement date around July 1, 1960. Living accommodation available at reasonable cost for single or married doctor. Apply in writing to Supervisor of Employment Services, Ontario Hydro, 620 University Avenue, Toronto, Ontario or telephone EMpire 8-6767, local 2-2297.

ASSISTANT with view to partnership for a busy three-man group of general practitioners in a south western Ontario town. Reply stating your qualifications, salary required, etc. to Dr. D. W. Clare, Essex, Ontario.

WANTED.—LOCUM TENENS for the months of May, June, July, August, September 1960 for Uranium City, Saskatchewan. Varied and busy practice. Salary, $700 per month, plus car, accommodation, transportation to and from, including fare for wife. Boating, excellent fishing, time off. Write directly to: Uranium Medical Clinic if available for all or portion of above time.

DOCTOR REQUIRED IN SPENCERVILLE—a thriving community centrally located in the St. Lawrence Valley on Highway No. 16. Financial assistance if necessary. Please contact G. M. Snyder. Box 87, Spencerville, Ontario.

RADIOLOGIST—full-time associate. Certified 500-bed general hospital on West Coast. Very active diagnostic and therapeutic department. Salary range $15,000-$18,000 per annum. Excellent perquisites—pension, health plan, cumulative sick leave and one month's holiday. State training, experience, availability, marital status, etc. Reply to Box 702, CMA Journal, 150 St. George St., Toronto 5, Ontario.

ASSISTANT MEDICAL OFFICER required for a rapidly growing rural-urban Health unit in Southern Ontario. Apply stating qualifications and references to Dr. A. F. Bull, Director and Medical Officer of Health, Halton County Health Unit, Ontario.

WANTED.—ASSOCIATE in general practice in a town of 2500 in Northern Minnesota, U.S.A. Salary or partnership. Good hunting and fishing. Surgical training would be beneficial but not necessary. Reply Box 706, CMA Journal, 150 St. George St., Toronto 5, Ontario.

WANTED.—Trained ophthalmologist to be associated with a group of board eligible physicians and surgeons. Work largely on fee for service basis. Apply Dr. J. M. Emmett, Chesapeake and Ohio Hospital, Clifton Forge, Virginia, U.S.A.

ASSISTANT PATHOLOGIST REQUIRED.—The Halifax Infirmary, Halifax, Nova Scotia, is in the process of expanding into a 460-bed general hospital. New laboratories will be built. An assistant pathologist is now required. Write—Administrator, Halifax Infirmary, Halifax, Nova Scotia.

THE WORKMEN'S COMPENSATION BOARD OF B.C. requires the services of a competent physician to review the treatment and progress of claimants, examine, or arrange for the examination of claimants when deemed advisable, assess the degree of permanent disability of claimants and to make recommendations on the medical aspects of claims. Must be licensed to practise in B.C. or prepared to obtain such license. Adequate experience in general practice and/or special qualifications necessary. Age preference 40-50. Superannuation and M.S.A. benefits. Reply by letter only please to: Personnel Manager, Workmen's Compensation Board, 707 West 37th Ave., Vancouver 13, B.C.

WANTED.—Locum Tenens for July and August and if possible until September 15th, 1960; to assist in an active general, partnership practice. A senior doctor will be present at all times to carry responsibility. Salary $700 per month, transportation also provided, if locum has own car, car allowance $50 per month. Applicants please state age, qualifications and experience. Apply to Drs. Cousineau & Foster, Castor, Alberta.

LOCUM TENENS.—Irish graduate 1957 available May 29 to June 19 Alberta or Saskatchewan. Accommodation for family. Own car. Reply before mid May to Box 715, CMA Journal, 150 St. George St., Toronto 5, Ontario.

PÆDIATRIC ASSISTANT—To busy pædiatrician, general practitioner or clinic. Class of 1947, married with family, Ontario licence. Reply to Box 716, CMA Journal, 150 St. George St., Toronto 5, Ontario.

ASSISTANT REQUIRED FOR GENERAL PRACTICE by July 1, 1960 in prosperous southern Ontario town of 2500 in association with well-established general practitioner. This office has had assistants for 13 years. Excellent vicinity for living, schooling, recreation (e.g. golfing, skating, curling, etc.) References must accompany applications. May consider locum tenens for July and August. Please state religion and salary expected. Reply to Box 626, CMA Journal, 150 St. George St., Toronto 5, Ontario.

WANTED.—Locum tenens for May, June, July, 1960. Two-doctor practice, one will always be in attendance. $700 per month plus expenses. Interested persons write or phone reverse, Dr. L. N. Gray, Preeceville, Saskatchewan, Phone 38.

GENERAL ROTATING approved internships available at Uniontown Hospital, Uniontown, Pa. Stipend—$350. per month. Graduates of Canadian Medical schools eligible. For further information, contact chairman, Intern Committee, Uniontown Hospital, Uniontown, Pa.

WANTED.—First of next July, doctor with a minimum of two years' training in Pædiatrics to relieve for one year. Write directly to the C. S. Williams Clinic, Trail, British Columba.

DOCTOR'S assistant required for busy general and surgical practice in northern Ontario town; small modern hospital with all modern facilities. Basic salary—$8000. minimum. Reply stating age, qualifications and race to Box 717, CMA Journal, 150 St. George St., Toronto 5, Ontario.

GENERAL PRACTITIONER.—to join well established general practitioner and general surgeon in growing southern Ontario community. Salary and car allowance leading to early partnership. Please reply with full information to Box 718, CMA Journal, 150 St. George St., Toronto 5, Ontario.

CANADIAN born doctor required as assistant. Good working conditions. Hospital. $10,000-$12,000 per annum. Reply to Box 719, CMA Journal, 150 St. George St., Toronto 5, Ontario.

ASSISTANT WANTED.—For busy general practice in south-western Ontario town. Nearby hospitals. Partnership later if mutually satisfactory. Modern office. Please state salary expected and enclose references. Reply to Box 720, CMA Journal, 150 St. George St., Toronto 5, Ontario.

WANTED.—Assistant with view to partnership for rural general practice in southwestern Ontario. Canadian or British graduate preferred. Both rural and hospital work will be included. Reply stating age, qualifications and experience to Box 721, CMA Journal, 150 St. George St., Toronto 5, Ontario.

GENERAL SURGEON-PHYSICIAN to join 2 young general practitioners in group practice. Surgical training necessary to complete group. Modern 40-bed hospital in progressive Ontario town of 5000. Would prefer recent graduate. Experience in practice not essential; will assist in equipping office. Reply to Box 722, CMA Journal, 150 St. George St., Toronto 5, Ontario.

WANTED.—Locum for July and/or August. General practice, no surgery. $700 per month, car expenses and use of house. Reply to Dr. C. E. Reed, Malartic, Quebec.

WANTED.—Two doctors, June 8th to September 15th. Must be single and have own automobile. For further particulars write to Dr. Pat Costigan, Banff, Alberta.

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BOOK REVIEWS

(Continued from page 804)

EMOTIONAL FORCES IN THE FAMILY. Edited by Samuel Liebman. 157 pp. J. B. Lippincott Company, Philadelphia and Montreal, 1959. $5.00.

Medicine is a peculiar profession. We are among the world's greatest advisers and when you think of it, the extent and amount of our advice is astonishing. From the first day that we go on the wards we find ourselves expected to advise even though our competence is meagre. As the years go on, this recurring expectation on the part of our patients encourages the most retiring of us to become —more or less—oracles. We feel obliged to advise. There is always a tendency, when one has done this long enough, to concentrate on the advice rather than on the advised. While this is understandable and indeed forgivable, it is a tendency which we would do well to scrutinize in large matters and in small.

It may be our generalized proclivity for advising which makes the present book so baffling to the critic. For, after asking himself what the book was about, he must then ask himself for whom it was written. From the extremely modest editorial preface one learns that this was a series of lectures at the Northshore Hospital, Winnetka, Illinois. The reticent editor gives us no further information about the nature of this hospital, nor are there any hints to be found about the nature of the audience. There are a few clues that can be derived from studying the nine lecturers, for they and the editor are all eminent psychiatrists. But the contents might have been given to psychiatrists, psychiatric residents or other residents at a refresher course for G.P.'s, while the back wrapper suggests that earlier volumes—but not, one hopes, this one—were intended for social workers and others in the mental health field. The dangers of giving highly specialized advice in a general way are clearly illustrated in this book. There is doubtless a place for medico-philosophical Jeremiads but two of them in the space of 150 pages is heavy going, for the other seven contributors are sandwiched between Dr. Joost Meerloo's "The development of the family in the technical age" and Dr. Lawrence Kubie's counterpointing the same theme in his "The disintegrating impact of modern life". One wonders what the effect of these gloomy essays can be on those unknown listeners who could not close the book as a reader can. One reader at least felt like those lines in Louis MacNeice's bagpipe music

> "The glass is falling hour by hour,
> The glass will fall forever.
> But if you break the bloody glass—
> You won't hold back the weather."

The other essays range from Dr. D. G. MacKerracher's very sensible contribution about the impact of ageing to some vague and unsatisfying meanderings about parental roles, one of which reads as if it had been taken directly from a tape recording. Possibly it was. To summarize, one might call this book "nine contributors in search of an editor". The extraordinary thing is that there must be a demand for books of this sort—great and successful publishing houses are not charities. Someone must read these essays

(Continued on page 30)


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BOOK REVIEWS

(Continued from page 26)

and pay to read them, but for whom were they intended and what will they get out of them? In larger matters too, we must remember that all men are not members of our particular branch of medicine—all men do not seek advice from us and do not see us as competent to give every sort of advice. At a time when the public is seeking guidance on many matters which affect us vitally, this test-tube example of our slapdash methods of advising should make us consider. This book was the result of ten able and intelligent people working together, but it is hard to find any central theme apart from a certain pessimism. Is that what they wanted to convey? Are human affairs really so much worse than they have ever been before? But that is what has been communicated at least to one reader. This is a book to ponder over—especially if one is concerned with the transmission of ideas.

HANDBUCH DER ORTHOPAEDIE. Band III, Obere Extremität (Handbook of Orthopaedics. Vol. III, Upper Extremities). G. Hohmann, M. Hackenbroch and K. Lindemann. 659 pp. Illust. Georg Thieme Verlag, Stuttgart, W. Germany; Intercontinental Medical Book Corporation, New York, 1959. $30.50.

The third volume of this handbook contains a comprehensive and scholarly presentation of the orthopædic diseases of the shoulder and upper extremity. Like the first two volumes it is of multiple authorship. In 17 chapters written by 11 contributors there are monographs on malformations, congenital diseases, and paralysis caused by poliomyelitis and by the lesions of peripheral nerves supplying this region. Inflammatory conditions, acute and chronic, and benign and malignant tumours are thoroughly covered. The presentation of injuries involving the soft tissues, articulations and bones is a large and very useful part of this book.

The intraarticular administration of hydrocortisone is highly recommended and the use of it is considered "free of any side effects, and without any contraindications" —a statement which sounds rather over-enthusiastic. Occasional repetition, admittedly hard to avoid in a work of this type and magnitude, was noted in this part.

This volume continues the high standard of the previous ones and the generous yet careful use of illustrations is maintained.

The fourth and last part which will deal with the lower extremities will appear shortly, and no doubt is eagerly awaited by all German-reading general and orthopædic surgeons who want this valuable storehouse of information on their bookshelves.

VOM SYMPTOM ZUR DIAGNOSE (From Symptom and Sign to Diagnosis). Edited by W. Hadorn, Berne, Switzerland. 866 pp. Illust. S. Karger, Basle and New York, 1959.

A book which attempts to trace the investigation of a patient from his leading symptom and signs to the final diagnosis is always regarded with favour by practitioners. The present volume is a magnificent contribution towards the study of symptoms and signs, and represents a co-ordinated piece of work by physicians in Denmark, Germany, Austria, Sweden and Switzerland. It is in the first place intended for general practitioners and for students in their final year. Since it must be remembered that the German word "Symptome" includes not only symptoms but signs, the subjects discussed fall under both categories. The writing reaches a high level, and an adequate attempt is made in most cases not only to discuss the differential diagnosis of a symptom or a sign, but to give a very adequate exposition of the pathology and physiology behind the subject and to make rational deduction possible.

Among the general symptoms discussed are the facial expression of the patient, cyanosis, jaundice, fever, loss of weight, obesity, œdema, and dehydration. The immense subject of pain has a special section to itself, and the rest of the book is made up of special symptoms and signs related to disorders of various systems. Thus, under the heading of respiratory disorders, there is a full discussion of dyspnœa, cough and sputum and hæmoptysis. Disorders of the skin, eye and ear are not forgotten, and there is a special chapter on the symptoms and signs associated with poisoning. A valuable appendix contains tables of normal values in clinical laboratory tests and incubation times. The individual chapters are supplied with a good bibliography, and there are a number of illustrations to lighten the text. The book itself is beautifully printed and produced, and will undoubtedly find ready sale among practitioners who can read German.

(Continued on page 36)

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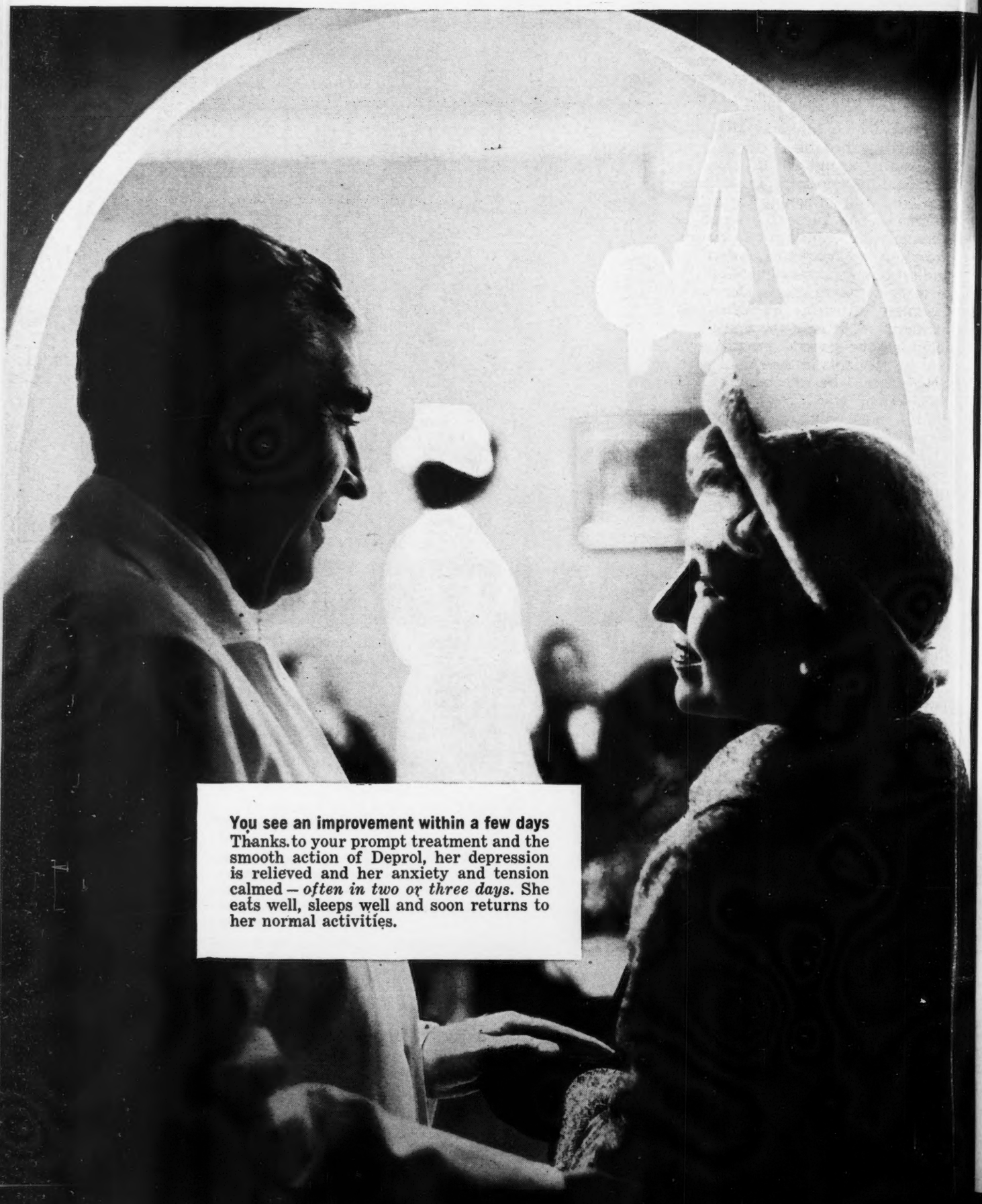

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BOOK REVIEWS

(Continued from page 31)

SENSITIVITY REACTIONS TO DRUGS. A symposium organized by the Council for International Organizations of Medical Sciences, under the joint auspices of UNESCO and WHO. Edited by M. L. Rosenheim and R. Moulton. 230 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $8.50.

This report of a symposium held at Liège in July 1957 has been edited by Professor M. L. Rosenheim and Dr. R. Moulton. The subject matter adheres very closely to the title and gives a broad survey of the hypersensitivity allergic reactions to drugs.

An attempt is made by the participants to deal with the reaction of the various parts of the hæmatopoietic system to different drugs, and they point out the possible mechanisms by which the hæmolytic reactions, the megaloblastic reactions, the thrombocytopenic reactions and the agranulocytic reactions are mediated.

Somewhat detailed studies are given of the antibodies to drugs, and among other interesting observations is the fact that a drug may form a complex with antibody without the necesssity of combining with a protein, suggesting that drugs may sometimes act as complete antigens without first combining with protein. The effects of drugs such as penicillin, chloramphenicol and hydralazine which are in fairly common use, are discussed in some detail.

In addition there is a general discussion of the early detection of drug sensitivity which points out that dangerous chemicals should be used only when they are essential and that one should seriously take note of a patient's statement that he is sensitive to a drug.

Drug sensitivity should not be tested by intradermal methods; it is not possible in the present state of knowledge to advise that regular blood counts can safely be omitted.

The contributors to the symposium include such well-known names as Dr. Merril W. Chase, Professor L. P. Garrod, Dr. Halpern, Dr. A. R. Rich and Dr. U. Serafini. The book provides a fairly full bibliography and is a good reference book on the subject.

MEDICAL NEWS *in Brief*

(Continued from page 789)

POSTGRADUATE COURSE IN EARLY DETECTION AND PREVENTION OF DISEASE

The American College of Physicians announces a postgraduate course for early detection and prevention of disease to be held May 9-13, 1960, at the University of Pennsylvania School of Medicine, Philadelphia, Pa.

Special emphasis will be placed upon the detection of disease before the development of readily recognized signs and symptoms. The early diagnosis and prevention of chronic pulmonary disease, bronchogenic carcinoma, degenerative joint disease, rheumatic fever, diseases of the thyroid, and emotional disorders will be dealt with.

Registration should be made through the Executive Offices, The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pennsylvania.

(Continued on page 38)

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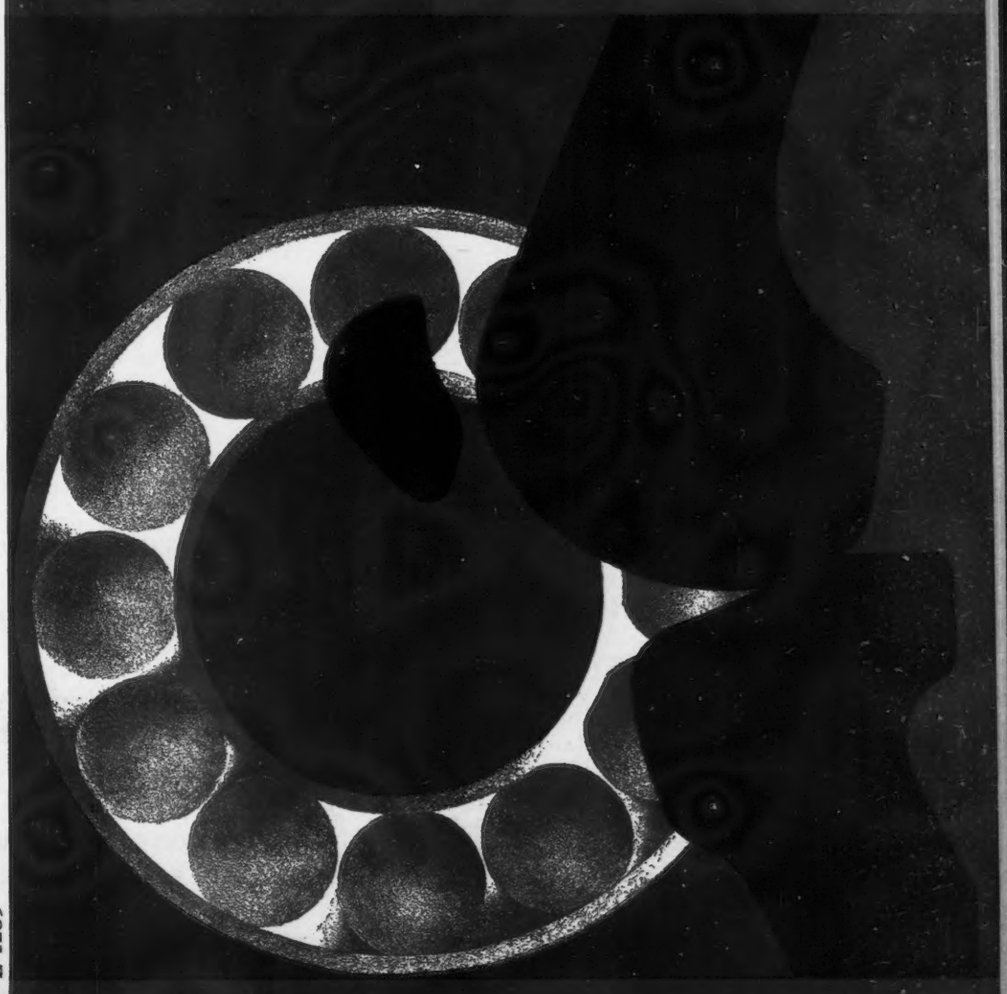

MEDICAL NEWS *in brief*

(Continued from page 36)

MARKLE SCHOLARS IN MEDICAL SCIENCE

The John and Mary R. Markle Foundation have announced the names of the 25 scholars whose appointments will begin on July 1, 1960. Among these are the following in Canadian universities: The University of Toronto Faculty of Medicine, John Robert Evans, M.D., D.Phil., resident and fellow; the University of British Columbia Faculty of Medicine, Vancouver, Joseph A. Hinke, assistant professor, currently research assistant, University College of London, England; McGill University Faculty of Medicine, Montreal, Charles H. Hollenberg, lecturer, currently research fellow, New England Center Hospital, Boston; the University of Manitoba Faculty of Medicine, James F. Lind, lecturer, currently fellow of the Mayo Foundation of Rochester, Minn.

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POSTGRADUATE COURSE IN CURRENT CARDIOVASCULAR RESEARCH

The American College of Physicians announces a postgraduate course in current research in cardiovascular disease to be held May 16-20, 1960, at the National Heart Institute, Bethesda, Maryland. The course is designed to give the internist a discussion of many of the facets of cardiovascular disease that are under investigation at the present time, with the research program of the Heart Institute serving as the basis for the presentations.

Registration should be made through the Executive Offices, The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pennsylvania.

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RADIATION HEALTH PROBLEMS AS THEY RELATE TO EPIDEMIOLOGY

Although recognized as an attribute of modern civilization, radiation exposure in the form of natural radiation has been present in man's environment since life first originated on the earth. The intensity of natural radiation reaching all living things is in the order of from three to six ten-thousandths of a roentgen per day, or somewhat higher, depending on location. Since the discovery of x-rays and radium, however, limited numbers of people have been exposing themselves to ionizing radiation levels above this amount.

Sporadic cases of injury were known early in the century, but studies in radioepidemiology were limited to that of the young women in the watch dial industry in New Jersey, and the pitchblende miners in Czechoslovakia. With the development of nuclear fission as a method of releasing energy and of producing vast quantities of radioactive materials, an extensive research program, begun under the Manhattan district, has been carried on under the auspices of the Atomic Energy Commission. More precise information on the biological effects of ionizing radiation is being sought.

This research program investigates the biological effects of exposure to radioactive materials deposited in the body, and that associated with external radiation. Studies have been initiated in different groups, as for example, persons who had been engaged in dial painting, and patients who had received radium internally. Other studies include the survey of the health status of the uranium miner by the United States Public Health Service, and the study of the Atomic Bomb Casualty Commission in Hiroshima and Nagasaki, Japan. New and more extensive studies are being planned in various countries with a view to discovering possible genetic, leukæmogenic, and other effects of radiation, including curtailed life-span.

After gross exposure the cause-and-effect relationship is established without too much trouble. The effects of chronic low level exposures present a more difficult problem. There are numerous biological and environmental factors whose action can be confused and compounded with any action that might be produced by the radiation exposure. Such studies call for careful methods as their design and execution constitute a challenge of the first magnitude.—C. L. Dunham, *Am. J. Pub. Health*, 49: 1607, 1959.

THE WORLD MEDICAL ASSOCIATION

The German Medical Association has extended a warm invitation to every doctor in the world to attend the XIVth General Assembly of the World Medical Association, and the 63rd Deutsche Arztetag in West Berlin, Germany, September 15 to 22, 1960. Those interested in receiving the latest details as to the program, accommodations and registration are invited to write to Dr. Josef Stockhausen, Haedenkampstrasse 1, Köln-Lindenthal, Germany.

POSTGRADUATE COURSE IN HYPERTENSIVE DISEASE

The American College of Physicians announces a postgraduate course in the procedures for diagnosis and therapy of essential, adrenal and renal hypertension to be held May 23-26, 1960, at the Massachusetts Memorial Hospitals, Boston, Massachusetts.

The course will consider the problems of hypertension from the moment of its recognition in a patient by physician, through its proper clinical classification made with the help of various diagnostic and prognostic procedures, and the selection of therapy including long-term management by all available means, both medical and surgical.

Registration should be made through the Executive Offices, The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pennsylvania.

NUTRITION AND ABSENTEEISM

It is pointed out in the Occupational Health Bulletin February 1960 that the importance of nutrition in relation to physical fitness and absenteeism is difficult to assess because both these terms

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MEDICAL NEWS *in brief*

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cover a variety of factors. Physical efficiency includes such factors as fatigue, training, skill and habit. It is reflected inversely in industry by accident, spoilage or inaccurate and unacceptable work and by decreased production. Absenteeism is explained in different ways by different people; the safety supervisor, the psychologist, the lighting engineer, each accounts for absenteeism in his own way.

It is important to remember that absenteeism results from many different causes and is only partly due to illness. The other causes of absenteeism may also be connected with nutrition, since nutrition has so many direct and indirect effects. For example, a lack of vitamin B_1 or thiamine in the diet may give a man digestive disturbances that will keep down his production all day; or it may affect his nerves so that he picks a quarrel with his neighbour and puts them both off production; or it may affect the sensitivity of his fingers so that he spoils more pieces. Since the B vitamins tend to occur together, the man may also lack riboflavin, which might give him sore, watery eyes in addition to the above symptoms, and this has been found to blur vision enough to cause an accident which no one would attribute to a nutritional deficiency.

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X-RAY APPEARANCE IN CHRONIC BRONCHITIS

Following recent renewed interest in chronic bronchitis in Great Britain and, more recently, in the United States, a case is reported by Oliva, Spradley and Williams (*Am. J. Roentgenol.*, 83: 274, 1960) demonstrating the two specific bronchographic findings associated with chronic bronchitis, i.e., bronchial gland involvement and bronchiolectasis. In the same journal, Sturtevant and Knudson reviewed 523 bronchograms and found 12 cases of bronchiolar ectasia (83: 279, 1960). Correlating these findings with the clinical picture, they found that all except one of the 12 cases had symptoms that could fit in with chronic bronchitis or bronchiectasis. All patients had been smoking heavily and only two had definite allergies. These reports seem to substantiate previously described findings of bronchiolectasis as being pathognomonic of chronic bronchitis.